Supplemental Readings

Global Health Week

Day 5

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Rehydration with soft drink-like beverages exacerbates dehydration and worsens dehydration-associated renal injury

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A MAJOR EPIDEMIC of chronic kidney disease is occurring in Central America among workers in the sugarcane fields. To date there have been reported to be over 20,000 deaths. While the etiology is unknown, most studies suggest that recurrent dehydration is a major risk factor (10, 15, 24, 32).

Subjects working in hot environments tend to lose both salt and water, but usually have a greater loss of water, leading to transient hyperosmolarity. Hyperosmolarity activates two major systems: vasopressin release from the posterior pituitary and the aldose reductase enzyme. Vasopressin has been shown to drive low grade renal injury and to exacerbate chronic kidney disease in laboratory animals (8). Likewise, the aldose reductase system converts glucose to sorbitol, which can then be converted to fructose, which is a substrate for fructokinase in the proximal tubule (11). In turn, the metabolism of fructose in the proximal tubule can result in tubular injury and the release of oxidants and inflammatory mediators (11, 28). Indeed, we recently reported that recurrent heat-associated dehydration could lead to chronic kidney disease in mice due to endogenous generation of fructose in the kidney from the aldose reductase pathway, and this was prevented in mice unable to metabolize fructose (fructokinase-knockout mice) (34).

The observation that fructose plays a role in dehydration-associated renal injury raises major concerns that rehydration with sugary beverages that contain fructose might worsen rather than help dehydration-associated renal injury. Furthermore, fructose has a peculiar ability to stimulate vasopressin release in humans that is not observed with other sugars such as glucose (42).

We therefore utilized a model of heat-induced dehydration to test the hypothesis that brief (2 h) rehydration with a soft drink beverage (consisting of 7.15% fructose-3.85% glucose similar to standard soft drinks) might worsen renal injury compared with rehydration with water or stevia containing water. Our studies raise serious concerns for the common practice, especially among adolescents and young adults, to drink soft drinks as a means to quench thirst following an episode of dehydration.

METHODS

Ethical Approval

This investigation was performed in accordance with the “Guide for the Care and Use of Laboratory Animals” published by the National Institutes of Health, and the Mexican Federal Regulation for animal experimentation and care (NOM-062-ZOO-2001) and for the disposal of biological residues (NOM-087-ECOL-1995).

Reagents

Chemicals were of reagent or higher grade from Sigma-Aldrich (St. Louis, MO) unless otherwise specified. Antiiurinary neutrophil gelatinase-associated lipocalin (N-GAL), antinephrin, antivasopressin V1a receptor, anti-superoxide dismutase (SOD)-1, anticalcatale, and anti-GPx anti-antibodies were purchased from Santa Cruz Biotech-
nology (Dallas, TX). Antifructokinase (KHK) and antialdose reductase were obtained from GenTex (Irvine, CA), antivasopressin V2 receptor antibody was obtained from Abcam (Cambridge, MA), and anti-β-actin antibody was obtained from Cell Signaling (Danvers, MA). Secondary antibodies conjugated with horseradish peroxidase were from Cell Signaling.

**Experimental Protocol**

*Heat-induced dehydration protocol.* Three groups of male Wistar rats were placed in a 36°C closed environment for 1 h without food and water from Monday to Friday during 4 wk. Thermal exposure is considered a valid model to induce dehydration in rats (2–6, 29–31). After heat-induced dehydration, animals were allowed to rehydrate for 2 h with either tap water (W, n = 6), a sweetened beverage made with an 11% of a fructose-glucose combination, which is a similar composition used in major brands of soft drinks (FG, 7.15% fructose and 3.85% glucose, respectively, n = 7) (10, 12), or water sweetened with the noncaloric edulcorant stevia (ST) (4 g/l water, Svetia, Metco Mexico, n = 7). Pelleted food was provided ad libitum. For the rest of the day and during weekends animals received tap water and food ad libitum. The loss of weight induced by heat and the amount of drinking fluid consumed during rehydration period were recorded daily.

**Normal control group (C).** This group consisted of five male Wistar rats of similar body weight and age. They received food and water ad libitum during 4 wk. The amount of water and food consumed were measured daily. Body weight was measured weekly.

**Measurements**

At the end of the 4-wk study period, systolic blood pressure was measured, and urine was collected for 18 h (overnight) in metabolic cages. Food was not provided during the urine collection. Rats were then euthanized by anesthesia with isoflurane and exsanguination. A blood sample was collected and centrifuged. Plasma and urine samples were frozen until further analyses. Both kidneys were perfusion washed with cold phosphate-buffered saline, and the right kidney was excised and divided into cortex and medulla, frozen in liquid nitrogen, and stored until further processing. The left kidney was fixed by perfusion with 4% paraformaldehyde for histology.

**Blood and Urine Analyses**

Plasma and urine osmolality was measured using a freezing point depression osmometer (Advanced Instruments, Norwood, MA). Plasma and urine creatinine were measured by a validated enzymatic method (22) and creatinine clearance was calculated. Plasma and urine urea nitrogen concentrations were analyzed by autoanalyzer (Instrumentation Laboratory, Bedford, MA). Sodium concentration was analyzed by flame photometry. Fructose was measured by a colorimetric assay (18), and uric acid was measured with a fluorometric kit (Amplex Red, Life Technologies, Carlsbad, CA). Plasma copropetin was extracted using Sep-pack C18 cartridges (Waters, Milford, MA) and then measured by a rat-specific competitive enzyme immunoassay (Peninsula Laboratories, San Carlos, CA).

Solute-free water reabsorption (T²H₂O) during the 18 h of urine collection was calculated accordingly to the following formula: T²H₂O = osmolar excretion – urine volume = (Uosm/Posm) × V – V, where Uosm and P posm are the urine and plasma osmolality, respectively, and V the urine volume collected in 18 h.

**Blood Pressure**

Systolic blood pressure (SBP) was measured in conscious rats by a validated volume-based tail-cuff method (17) at the end of the follow-up.

**Evaluation of Markers of Tubular Damage**

For the determination of N-acetyl-β-D-glucosaminidase (NAG) activity in urine samples, 4-nitrophenyl-N-acetyl-β-D-glucosaminide was used as a substrate.

Neutrophil gelatinase-associated lipocalin (NGAL) expression, a sensitive marker of renal proximal tubule damage (25), was evaluated by Western blotting. Renal cortex proteins were extracted using a mitogen-activated protein (MAP) kinase lysis buffer, as previously described (33), and incubated with a primary antibody against NGAL (Santa Cruz Biotechnology) at 4°C overnight, using β-actin antibody (Cell Signaling) as load control.

**Renal Cortex Content of Fructose and Uric Acid**

Fructose was extracted from cortical renal tissue by perchloric acid precipitation, and its concentration was measured by the anthrone-based colorimetric method (18). Uric acid (UA) is a by product of fructose catabolism in tissues expressing KHK and is associated with its detrimental effects (21). Therefore, tissue UA was measured both as a marker of renal damage and also as a surrogate of fructose increased metabolism. UA was extracted as previously described (11). UA was measured using Amplex Red assay kit (Life Technologies). Fructose and UA concentrations were normalized by protein concentration.

**Renal Cortex Markers of Oxidative Stress**

Tissue was homogenized in phosphate buffer containing a cocktail of protease inhibitors. Protein carbonyls and lipid peroxidation (4-hydroxynonenal, 4-HNE) were measured using previously published methods (27, 39) and normalized by protein concentration.

NOX4, catalase, glutathione peroxidase, and superoxide dismutase-I protein expression. Renal cortex proteins were extracted using a MAP kinase lysis buffer, as previously described (22). Each of the following primary antibodies were incubated at 4°C overnight: anti-NOX4 (GeneTex, Irvine, CA), antiacatalase, -GPx, and anti-SOD-1. Protein loading was controlled with an anti-β-actin antibody (Cell Signaling). Chemiluminescence was captured using Clarity horseradish peroxidase chemiluminescence kit (Bio-Rad, Hercules, CA) and exposure of membranes over X-ray film inside a standard developing cassette. Film was developed manually and exposure was repeated varying the time as needed for optimal detection; thereafter the film was scanned. Blots were recorded, and densitometry was performed using the Image Studio Lite Software (Licol, Lincoln, NE).

Aldose reductase, KHK, and vasopressin V1a and V2 receptors protein expression by Western blot analysis. Renal cortex proteins were extracted using a MAP kinase lysis buffer, as previously described (33). Each of the following primary antibodies were incubated at 4°C overnight: anti-KHK (GeneTex, Irvine, CA), antialdose reductase (GeneTex), antivasopressin V1a receptor (Santa Cruz Biotechnology), antivasopressin V2 receptor (Abcam), and anti-β-actin antibody (Cell Signaling). Chemiluminescence was recorded and quantified using the Image Studio Lite Software (Biotech, Lincoln, NE).

**Histological Analysis**

Fixed renal tissue was embedded in paraffin and processed accordingly. The evaluation was performed blinded. Sections were stained with periodic acid-Schiff’s stain (PAS). Glomerular changes (glomerulosclerosis or hypoperfusion as evidenced by wrinkling and collapse of the glomeruli) were qualitatively evaluated. Tubulointerstitial cellular infiltration was studied in PAS-stained sections taking advantage that the nucleus of inflammatory cells is stained in dark blue. The number of inflammatory cells were quantified in 20 nonoverlapping fields at ×400 magnification and expressed as positive cells in 20 fields.
Statistical Analysis

Values are expressed as means ± SD. One-way ANOVA determined significant differences between groups. When the ANOVA P value was <0.05, posttest comparisons were made using Sidak’s multiple-comparison test assuming an αPF (per family of tests) = 0.05. Each computed P value was adjusted to account for six multiple comparisons per family. The possible relationship between variables was tested by correlation analysis. Statistical analysis was performed with Prism version 6.05 (Graph Pad Software, San Diego, CA).

RESULTS

Dehydration Protocol

The central hypothesis of this study was that rehydration with fructose/glucose concentrations similar to that observed in soft drinks might accelerate heat-induced dehydration renal injury. Heat-induced dehydration was performed by exposure of rats daily to heat (1 h at 36°C) followed by 2 h of ad libitum rehydration with either water of a fructose-glucose (FG) solution similar in composition to that present in soft drinks. The rest of the 24-h period all groups only received water for fluid intake. Because rats drank more FG solution than regular water, we also included a group given stevia water, as rats drank the same amount of stevia water as FG water thus providing a control for fluid intake following the dehydration procedure. These three groups were than compared with normal control rats that were not exposed to heat.

Effects on Weight and Fluid Intake

Heat-induced dehydration resulted in equivalent mean daily body weight loss among the three groups (water, stevia, and FG) at the end of the heat period (Table 1). During the 2-h ad libitum rehydration period, rats administered FG and stevia water drank more fluid (~30%) compared with water alone.

Table 1. Fluid consumption, plasma and urine parameters, and systolic blood pressure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Control (n = 5)</th>
<th>Heat-Induced Dehydration</th>
<th>Heat-Induced Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beverage</td>
<td></td>
<td>W (n = 6)</td>
<td>FG (n = 7)</td>
</tr>
<tr>
<td>Mean fluid drunk during rehydration, ml/2 h</td>
<td>24 ± 0.3</td>
<td>9 ± 0.1</td>
<td>12 ± 1.1B</td>
</tr>
<tr>
<td>Mean BW loss after HD, % BW</td>
<td>1.7 ± 0.2</td>
<td>33 ± 1.0A</td>
<td>34 ± 0.9A</td>
</tr>
<tr>
<td>Mean total fluid consumption, ml/24 h</td>
<td>22 ± 3</td>
<td>0.93 ± 0.07</td>
<td>1.73 ± 0.13A,B</td>
</tr>
<tr>
<td>Urea, mg/dl</td>
<td>20 ± 2</td>
<td>0.85 ± 0.12</td>
<td>0.93 ± 0.07</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.89 ± 0.14</td>
<td>0.80 ± 0.20</td>
<td>1.14 ± 0.04A,B</td>
</tr>
<tr>
<td>Fructose, µg/ml</td>
<td>0.28 ± 0.15</td>
<td>0.50 ± 0.19</td>
<td>0.50 ± 0.19</td>
</tr>
<tr>
<td>UA, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>15 ± 6</td>
<td>28 ± 6A</td>
<td>19 ± 4B</td>
</tr>
<tr>
<td>Urine flow, µl/min</td>
<td>166 ± 24</td>
<td>437 ± 131A</td>
<td>652 ± 106A,B</td>
</tr>
<tr>
<td>Creatinine, mg/18 h</td>
<td>11 ± 2</td>
<td>10 ± 2</td>
<td>11 ± 1</td>
</tr>
<tr>
<td>Fructose, µg/18 h</td>
<td>21 ± 9</td>
<td>41 ± 11A</td>
<td>30 ± 7</td>
</tr>
<tr>
<td>UNa, meq/18 h</td>
<td>0.29 ± 0.13</td>
<td>1.81 ± 0.32A</td>
<td>4.91 ± 1.21A,B</td>
</tr>
<tr>
<td>CrCl, ml/min</td>
<td>1.24 ± 0.1</td>
<td>1.01 ± 0.13</td>
<td>0.60 ± 0.06A,B</td>
</tr>
<tr>
<td>FENa, %</td>
<td>0.12 ± 0.05</td>
<td>0.87 ± 0.16A</td>
<td>3.6 ± 1.1A,B</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>116 ± 7</td>
<td>143 ± 3A</td>
<td>139 ± 7A</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, number of rats. BW, body weight; SBP, systolic blood pressure; CrCl, creatinine clearance; UNa, sodium excretion. FENa, fractional sodium excretion. Statistical comparisons: A vs. normal control. B vs. Water. C vs. FG.

Rats underwent blood testing in the morning after having ample time to be rehydrated. Despite daily rehydration, rats that had been exposed to daily heat showed higher mean levels of plasma and urine osmolarity with higher plasma copeptin levels compared with normal control rats (Fig. 1). Nevertheless, rats hydrated with FG showed significantly higher plasma and urine osmolality and higher copeptin levels and higher free water reabsorption by the kidneys despite greater fluid intake during the 2-h rehydration period (Fig. 1). In contrast, rehydration with stevia water was associated with lower plasma osmolality and lower copeptin levels than that observed with water alone.

Heat-induced dehydration raised absolute sodium urine excretion and sodium fractional excretion; this effect was enhanced in FG-rehydrated group. In contrast, in rats rehydrated with stevia the rise in sodium excretion, both absolute and fractional, was prevented (Table 1).

Heat-induced dehydration alone also increased blood pressure compared with normal control rats. Rehydration with FG did not further raise blood pressure. Stevia rehydration was associated with lower blood pressure than the group rehydrated with water (Table 1).

In summary, recurrent and transient heat-induced dehydration results in some persistent evidence for dehydration (elevations in plasma and urine osmolarity, elevated copeptin levels) and this is significantly worse in rats rehydrated with FG solutions.

Renal Injury Induced by Dehydration is Worsened by Rehydration With Soft Drink

No differences in plasma urea were observed in these four groups as measured in the fasting morning blood samples. However, rehydration with FG solutions to heat-exposed rats...
significantly increased plasma creatinine and decreased Cr clearance (Table 1).

We evaluated two markers of proximal tubule damage: NAG urine excretion and the expression of NGAL. In rats that received FG as rehydration fluid there were significant increments in the excretion of NAG in urine and in NGAL renal cortex expression. Rehydration with stevia prevented those changes (Fig. 2A).

We also evaluated whether renal structural damage was already present. Dehydrated rats with FG rehydration had significantly more glomerular hypoperfusion and glomerulosclerosis compared with water and stevia rehydration (Fig. 2B). Mild tubulointerstitial inflammation was also observed in the group that received FG.

These data document that heat-induced dehydration is associated with both structural and urinary biomarker evidence of renal injury and this is worsened with hydration using FG solutions.

**Potential Mechanisms for Renal Injury: Aldose Reductase-Fructokinase-Uric Acid Pathway and the Vasopressin Pathways**

We also measured uric acid and fructose as both may be induced by dehydration [by renal retention of uric acid coupled with increased generation of both fructose and uric acid via the aldose reductase pathway (34)]. As expected, heat-induced dehydration was associated with a numerical rise in plasma uric acid and a significant rise in urine fructose, although no change in plasma fructose from normal controls was observed (Table 1). In contrast, rehydration with FG was associated with similar rise in plasma uric acid and control heat-dehydrated rats, but with higher plasma levels, despite that urine levels were found similar to water rehydrated rats. Stevia-treated rats showed lower plasma uric acid and comparable levels of plasma and urine fructose as control rats.

In renal cortex of rats that received water as rehydration fluid, concentrations of fructose and uric acid were not different compared with normal control rats (Fig. 3). On the contrary, rats that received FG during rehydration period, a significant increment in the concentration of fructose and uric acid were observed. In stevia-rehydrated groups, fructose and uric acid renal concentrations remained comparable to water rehydrated and control groups (Fig. 3).

As activation of fructokinase-uric acid pathway is associated with increased oxidative stress via activation of NOX4 (23, 35, 37, 44), we also evaluated lipid peroxidation and protein oxidation in renal cortex (Fig. 3). Heat-dehydrated rats that received water as rehydration fluid showed a slight but significant increment in lipid peroxidation and protein oxidation in renal cortex (Fig. 3). The increased content of fructose and uric acid induced by rehydration with FG was associated with a significant augmentation in oxidative stress as noted by a further increase in lipid peroxidation and protein oxidation. Stevia rehydration was associated with lower oxidative stress compared with FG groups. In agreement with the increment in oxidative stress observed in dehydrated rats rehydrated with FG beverage, we also observed significant overexpression of NOX4 as well as the antioxidant enzymes catalase, glutathione peroxidase (GPx), and SOD-1 in the kidneys (Fig. 3).

We also evaluated the renal cortex expression of the enzymes involved in fructose-uric acid pathway and vasopressin receptors (Fig. 4). Rats that the received water as rehydration fluid showed a slight but significant increment in the expression of aldose reductase in renal cortex. In parallel to the further increment in cortex fructose, uric acid and oxidative stress, the group of dehydrated animals that received FG for rehydration showed a significant increment in the expression of fructokinase, vasopressin receptors 1a and 2, and a further increase in the expression of aldose reductase. In contrast, rats that received stevia did not showed those changes (Fig. 4).
DISCUSSION

In this study, we tested the hypothesis that the type of rehydration solution might influence renal outcomes associated with recurrent mild dehydration. Specifically, we hypothesized that short-term rehydration with sugary beverages containing fructose might have adverse effects on the kidney. To test this hypothesis, we performed studies in a model of thermal dehydration and compared water, stevia-containing water, and a solution of fructose-glucose that is similar in composition to standard soft drinks. The present study shows that short-term rehydration with a FG sugary beverage after a mild dehydration stimulates the two systems that have been implicated in kidney injury, i.e., vasopressin (1) and aldose reductase-fructokinase activities (34). After rehydration with a fructose-rich beverage, we observed a greater renal oxidative stress and mild renal injury (glomerular and tubular alterations). In contrast, rehydration with plain water or with the noncaloric edulcorant stevia did not produce such deleterious effects.

Fructose is a substrate for fructokinase that is present in the proximal tubule, and a 60% fructose diet in rats can induce modest tubular injury (11, 28). Fructose infusion in humans
can also stimulate vasopressin release, whereas an equimolar solution of glucose does not (42). Our basic hypothesis was that recurrent stimulation of these pathways might induce renal disease and that hydration with fructose-containing solutions could increase vasopressin release and provide a substrate for fructokinase that might lead to further renal damage.

The type of rehydration fluid had significant effects on most of the outcomes. The administration of FG but not that of ST as rehydration fluid resulted in a further and significant increment in plasma copeptin. Moreover, rats continued to show signs of dehydration with higher urine osmolality and increased free water reabsorption, likely due in part to increased urinary sodium excretion observed in the FG-rehydrated rats. The evidence for worse dehydration despite increased fluid intake compared with the water-only group was striking. The consequence was also a greater renal oxidative stress, renal tubule injury, and subtle inflammatory infiltration. An additional marker of renal impairment in fructose-rehydrated rats was a significant fall in creatinine clearance. This finding suggests that glomerular filtration was reduced in this condition. However, it cannot be excluded that the observed differences in the creatinine clearances are due to different renal handling of creatinine by organic anion and/or cation transporters (16, 40).
An effect of a beverage containing simple sugars as replacement fluid was a significant increase in the accumulation of fructose and uric acid in the renal cortex. In previous studies, we and others have reported that tissue accumulation of uric acid is associated with augmented oxidative stress and damage (12, 26, 35). The results of the present studies are in agreement with those previous works.

Dehydration tended to increase systemic blood pressure in W and FG- but not in ST-rehydrated rats. This effect may be a consequence of increased renal oxidative stress in those groups (41). Whether this adverse influence of the rehydration fluid on SBP participated in kidney damage deserves further investigation.

We have previously shown that recurrent exposure to heat can induce renal injury through a fructokinase-dependent mechanism. In that study, the dehydration procedure was severe (34). We have also shown that a 60% fructose diet induces renal damage in the course of 8 wk (36). Moreover, rats that received a similar FG beverage ad libitum developed mild renal damage; however, those animals ingested ~80 ml of this fluid per day (39) in contrast to the present study in which rats had a limited consumption of this sweetened beverage (12 ml/day). It was also observed that rats that received a similar daily amount of fructose/glucose beverage (14 ml/day) but without dehydration did not develop renal alterations (data not shown). Therefore, the power of the current study is that the renal injury was found even with very mild recurrent dehydration when short-term rehydration with fructose-containing beverages was provided.

An interesting finding in this study was that dehydration was associated with increased urinary sodium excretion and that this was worsened by the rehydration with FG. Although volume contraction is known to cause a prerenal state with a decrease in fractional excretion of sodium, dehydration-induced hyperosmolarity can cause a mild natriuresis (known as dehydration natriuresis) (13). The signaling mechanisms (Sgk1 and TonEBP) involved in causing dehydration-induced natriuresis are the same as those known to stimulate the aldose reductase-fructokinase pathway and thus may account for the potentiation of this mechanism with the FG solutions (13, 43).

It was also observed a significant increase in urinary urea excretion in FG-rehydrated animals. We do not have a definite explanation for this effect; however, a mechanism that might contribute to increased urea excretion could be an overall increase in proteolytic activity induced by dehydration (9). Thus cellular dehydration is believed to be a driving force for proteolytic activity.

![Fig. 4. Renal cortex aldose-reductase, fructokinase (KHK), vasopressin V1a and V2 receptors expressions in mildly dehydrated animals induced by heat exposure in animals rehydrated for 2 h with water (W), an 11% fructose-glucose beverage (FG), and water sweetened with the noncaloric edulcorant stevia (ST). Statistical comparisons: A vs. normal control; B vs. water; C vs. FG.](image-url)
behind the severe protein wasting observed within the liver and skeletal muscles of extremely ill patients (19).

There is evidence that water intake is decreasing in the general population (20). Taking into account that, at present, a common practice is to rehydrate with sugary beverages when the threshold of mild dehydration has been reached (a situation in which vasopressin secretion is already increased), these findings might provide evidence for a pathophysiological mechanism that partially explain the association between sugary beverages consumption and renal damage (7, 14, 38).

Finally, stevia solution used as rehydration fluid prevented the rise in vasopressin secretion and preserved plasma and urine osmolality to normal levels. In addition, stevia-rehydrated animals had normal blood pressure and no evidence of renal tubule damage. It is not possible to know if this protective effect is due to a significantly higher volume ingested for rehydration in the stevia groups than in the plain water groups or if it is an effect induced by stevia itself.

In conclusion, this study shows that short-term rehydration with fructose-containing beverages in rats undergoing mild recurrent dehydration results in enhanced renal injury in association with greater stimulation of the vasopressin and polyol-fructosekinase pathways. The simultaneous triggering of both systems was associated with increased urinary concentration, oxidative stress, renal injury, and systemic hypertension. On the other hand, increased ingestion of fluids devoid of simple sugars (plain water or stevia solution) prevented the stimulation of vasopressin induced by mild dehydration.

Perspectives and Significance

This study is relevant to the epidemic of chronic kidney disease (CKD) in Central America, in which sugarcane and other workers are developing CKDs associated with recurrent heat-associated dehydration. However, it may also be an important factor in the high frequency of CKD that is occurring in hot climates such as Mexico and the southern United States. Further studies investigating the mechanisms involved in this injurious process are warranted in the future.

GRANTS

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DISCLOSURES

R. J. Johnson and M. A. Lanasca are listed as inventors on patent applications related to blocking fructose metabolism as a means to prevent acute and chronic kidney disease. R. J. Johnson, C. Roncal-Jiménez and L.-G. Sánchez-Lozada are members of Colorado Research Partners. F. E. García-Arroyo, M. Cristóbal, A. S. Arelano-Buendia, H. Osorio, E. Tapia, V. Soto, L. Bankir, and M. Madero have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS


REFERENCES


Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador – A cross-shift study of workers at risk of Mesoamerican nephropathy

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Abstract

Background: An epidemic of progressive kidney failure affects sugarcane workers in Central America. Repeated high-intensity work in hot environments is a possible cause.

Objectives: To assess heat stress, dehydration, biomarkers of renal function and their possible associations. A secondary aim was to evaluate the prevalence of pre-shift renal damage and possible causal factors.

Methods: Sugarcane cutters (N=189, aged 18–49 years, 168 of them male) from three regions in El Salvador were examined before and after shift. Cross-shift changes in markers of dehydration and renal function were examined and associations with temperature, work time, region, and fluid intake were assessed. Pre-shift glomerular filtration rate was estimated (eGFR) from serum creatinine.

Results: The mean work-time was 4 (1.4–11) hours. Mean workday temperature was 34–36 °C before noon, and 39–42 °C at noon. The mean liquid intake during work was 0.8 L per hour. There were statistically significant changes across shift. The mean urine specific gravity, urine osmolality and creatinine increased, and urinary pH decreased. Serum creatinine, uric acid and urea nitrogen increased, while chloride and potassium decreased. Pre-shift serum uric acid levels were remarkably high and pre-shift eGFR was reduced (< 60 mL/min) in 23 male workers (14%).

Conclusions: The high prevalence of reduced eGFR, and the cross-shift changes are consistent with recurrent dehydration from strenuous work in a hot and humid environment as an important causal factor. The pathophysiology may include decreased renal blood flow, high demands on tubular reabsorption, and increased levels of uric acid.

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1. Introduction

A devastating and lethal epidemic of chronic kidney disease (CKD) of undetermined origin has been present in the coastal lowlands of El Salvador at least since 1999 (Trabanino et al. 2002). The disease is not limited to El Salvador; it has been documented throughout many areas of the Pacific Ocean’s coast, from southern Mexico to Costa Rica (Brooks et al., 2012; Weiner et al., 2013; Ramírez-Rubio et al., 2013b; Wesseling et al., 2014; Correa-Rotter et al., 2014). The disease has been labeled the Mesoamerican Nephropathy (MeN) and is prevalent in male agricultural laborers, especially sugarcane cutters (Correa-Rotter et al. 2014). MeN is initially asymptomatic with limited or no proteinuria, but usually leads to end-stage renal disease. Common risk factors such as diabetes or hypertension are usually absent (Wesseling et al., 2014; Correa-Rotter et al., 2014). The limited data from kidney biopsies show tubular atrophy, interstitial fibrosis, and global glomerulosclerosis, often with an ischemic component (Wijkstrom et al., 2013; Lópe-Marín et al., 2014).

Many hypotheses have been proposed to explain the epidemiological, clinical and histopathological pattern of the disease, including pesticides, heavy metals, infections, or other regional environmental factors (Trabanino et al., 2002; Wesseling et al., 2014; Correa-Rotter et al., 2014; López-Marín et al., 2014; Gracia-Trabanino et al., 2005), self-medications (Wesseling et al., 2014; Ramírez-Rubio et al., 2013a), and heat exposure (Peraza et al., 2012; Brooks et al., 2012; Crowe et al., 2013; Wesseling et al., 2014; Correa-Rotter et al., 2014). Currently, repeated high-intensity work in a hot environment with dehydration is believed to be a key causal factor (Johnson et al., 2014), although the specific pathophysiology has not been clarified. Potential mechanisms suggested include subclinical rhabdomyolysis (Paula Santos et al. 2014), hyperosmolality-induced activation of the aldose reductase pathway in the kidney (Roncal Jimenez et al. 2014), vasopressin effects, and effects of hyperuricemia (Knochel and Dotin 1974).

Little is known about the impact on the kidney of short-term physiological changes of intense work in very hot conditions. We therefore performed a cross-shift study in sugarcane cutters in El Salvador. The overall aim was to contribute to the knowledge about risk factors for MeN in sugarcane workers and potential preventive measures. The specific aims were to assess heat stress and dehydration, as well as biomarkers of renal function and their possible associations with heat stress. A secondary aim was to evaluate the prevalence of pre-shift renal damage and possible causal factors.

2. Methods

2.1. Setting and study design

The study, executed by the Agency for Agricultural Health and Development, AGDYSYA, of El Salvador, was conducted in three groups of sugarcane cutters working in different regions in El Salvador: one located in a higher region at about 400 m above sea level, one at medium altitude at about 265 m altitude, and the third in the coastal region at sea level, all cutting cane for the same mill. The workers in the higher region were hired directly by the sugar mill, workers from the coast region were subcontracted, whereas the workers at medium altitude belonged to a cooperative. The a priori hypothesis was that workers in the coastal region would be more affected by heat stress.

The design is cross-sectional (in March/April 2014, at the end of the 6 months sugarcane cutting season), as well as a study of cross-shift changes. Each worker was examined on the same day before work (from about 05:30 AM) and after end of work (usually before noon, but in some cases not until 4 PM). The examinations were performed over 8 workdays, 12–32 workers per day.

2.2. Participants

In each of three regions, one sugarcane field was randomly selected among fields available according to the list of the sugar mill and its associated cooperatives. In each field there were groups of workers (cutting squads). The field supervisors provided lists of cutting squads and their members. In the coastal field, three cutting squads were selected randomly and in the higher altitude field two squads. In the medium altitude field there were only two cutting squads, and both were selected. From the lists of workers in these squads, workers were randomly selected, approached and checked against inclusion criteria until about 30 workers in each squad had been recruited. Inclusion criteria were age less than 50 years, and working as a full time cutter. In total 226 workers < 50 years were eligible and approached, and 189 of these agreed to participate and were recruited into the study (84% participation).

All participants signed a written informed consent to participate in the study, in accordance with the Declaration of Helsinki. The study was approved by the National Committee of Ethics for Clinical Research of the Superior Council of Public Health, El Salvador. The participants were aware that temperature and water intake was an important part of the study.

2.3. Work environment

Workers generally wore long pants and long sleeves. Many wore sandals or plastic shoes, while some wore boots. A shin guard was used to protect from machete cuts—other protective gear, including hats, gloves, handkerchiefs, glasses, etc. were rare (Fig. 1). On seven of the eight days, the Wet Bulb Globe Temperature (WBGT) was recorded every half hour during the whole work day in the fields at 1.25 m above the ground using two 800036 WBGT (Sper Scientific, China) handheld devices simultaneously (for quality assurance), and the mean of the results of the two devices was used. Temperature and relative humidity were measured in the fields using a Lascar Electronics data logger (EL-USB-2-LCD equipment, LASCAR, China), and the data were used to calculate the Heat Index (HI) used by the US Occupational Safety and Health Administration (OSHA) (OSHA, 1999; OSHA, 2014). For temperature, WBGT, and HI the means were calculated from the start of work until noon. The workers brought their own water for the work-day, and in the higher field the mill also provided additional water via a water-truck, although many workers did not like the taste or found it to be too far away.

2.4. Medical examinations

Examinations were performed in tents located at the entrance to the sugarcane fields. Trained nurses and doctors from the AGDYSYA team used a structured interview to ask workers about use of tobacco, alcohol, prescribed and non-prescribed medications (pictures of drug packages shown), previous work history, including pesticides commonly used in the region, symptoms, and liquid intake on that day. Body weight, blood pressure, pulse rate, and blood (venipuncture) and urine samples were collected before and after the work-day. Liquids for personal intake on the work-day were weighed before and after shift.

Body weight was measured with minimal clothing (underwear) using SECA electronic AD 769 scales (Seca, Birmingham, UK). Blood pressure was measured in the sitting position using a digital system (Omron HEM 7220, Omron Healthcare Inc., Bannockburn, IL, USA), which also recorded the pulse rate.
The participants were asked to perform their work in the sugarcane fields as they would do on a typical day. At the end of the work-day, all medical examinations and blood and urine collection were repeated, and a post-shift questionnaire was applied about work characteristics during the day such as number of hours worked, liquid intake (amount and type, at home and during work), and amount of cane cut.

2.5. Blood and urine sampling, and biochemical analyses

Blood samples were collected in vacuum tubes, which were centrifuged in the field after 30 min for separation of serum, placed in coolers and transported to a local laboratory where they were aliquoted and analyzed (see below) on the same day. Aliquots were frozen (−20°C) and sent about six weeks later to the University of Colorado in Denver for some duplicate and extra analyses (see below). Urine was collected in sterile polypropylene tubes, and aliquots were collected into cryotubes with and without preservative; one portion was centrifuged in the field and examined in situ (see below) and the rest was transported in the coolers to the local laboratory. At the laboratory urines aliquots were frozen (−20°C) and sent to Denver together with the serum samples, and later to the University of Gothenburg.

Hemoglobin and hematocrit in whole blood were determined by standard routines at a local laboratory as were serum samples for glucose, creatinine, uric acid, sodium, potassium, chloride, magnesium, ionized calcium, and liver aminotransferase (alanine and aspartate) enzymes. Serum butyryl cholinesterase was measured using a cholinesterase (PTC) reagent set (kinetic procedure) from TECO DIAGNOSTICS (TC). In addition serum samples were analyzed at the laboratory in Denver for serum urea nitrogen, and osmolality (freezing point method; Micro-Osmometer), and for creatinine, uric acid, and sodium levels using the VetAce automated biochemistry machine (Alfa Wassermann, West Caldwell, NJ). Uric acid was determined using uricase, and sodium using an ion selective electrode. Creatinine was determined using an alkaline picrate rate method, and adjusted to standardized creatinine, calibrated against creatinine determined by isotope dilution mass spectrometry. Serum urea nitrogen (BUN) was determined using the ACE Alera clinical chemistry system (Alfa Wassermann, West Caldwell, NJ). Serum creatine phosphokinase (CPK) was analyzed in a random subgroup of 30 workers before and after shift using human ELISA kit (BM ASSAYS, Beijing, China). Estimated glomerular filtration rate (eGFR) per 1.73 m² of body surface area was calculated using the EPI-CKD formula based on serum creatinine.

Urine samples were analyzed semi-quantitatively in the field with dip-sticks for protein, blood, glucose, and specific gravity (Dirui, Changchun, China), as well as albumin (Cypress Diagnostics, Langdorp, Belgium). Sediments were examined for cells, casts, and crystals. The aliquots shipped to the Denver laboratory were analyzed for creatinine, sodium, total protein, and neutrophil gelatinase-associated lipocalin (NGAL). NGAL was analyzed using a commercial ELISA kit (Abcam, MA, USA), according to the manufacturer’s instructions. Specific gravity was measured with a Ceti Digit 012 refractometer (Medline, Oxfordshire, UK), and pH with pH-sensitive electrode (Metrohm AG, Switzerland) at University of Gothenburg, Sweden.

2.6. Statistics

Differences between groups were tested with analysis of variance, t-test, Wilcoxon rank sum test (for variables not normally distributed), or Fisher’s exact test (for categorical variables). Differences between pre- and post-shift characteristics were tested by paired t-tests or by Wilcoxon’s signed rank test (for variables not normally distributed). Associations between variables were assessed by multiple linear regression (continuous variables) or logistic regression models (occurrence of reduced eGFR). When assessing the impact of environmental factors on cross-shift changes in blood pressure, blood, serum or urine biomarkers, the same model was used for all outcomes; predictors were WBGT, liquid intake per hour, work-time (in hours), and region. The rationale for this model was that temperature, work time and liquid intake were the main a priori factors believed to have an effect on hydration status and renal function. As WBGT was only measured seven out of 8 days, only 174 out of 189 participants were used in these models. Analyses were performed using SAS V.9.3 (SAS Institute, Cary, NC).

3. Results

Characteristics of the 189 sugarcane cutters are shown in Table 1. The mean age was 30 years, 89% were men, and about half of them never-smokers. Half of them worked as sugarcane cutters for at least five previous harvests. Few had a physician’s diagnosis of diabetes (N=2) or hypertension (N=4). Musculoskeletal pain was relatively common, and many had used acetaminophen and NSAIDS, at least occasionally (Table 1). Differences between workers from the three regions were small.

3.1. Work conditions

Workers generally wore long pants and long sleeves. The mean temperature from start of work until noon varied between 33.7 and 36.0°C during the seven measurement days and wet bulb
Table 1
Characteristics of the study population of 189 sugarcane cutters in three different sugarcane fields.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Higher alt. (N=55)</th>
<th>Medium alt. (N=41)</th>
<th>Coast (N=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, N men/women</td>
<td>168/21</td>
<td>52/3</td>
<td>38/3</td>
<td>78/15</td>
</tr>
<tr>
<td>Age, years (mean)</td>
<td>30 (18–49)</td>
<td>30 (18–49)</td>
<td>30 (18–49)</td>
<td>30 (18–49)</td>
</tr>
<tr>
<td>Body weight, pre-shift, kg (mean)</td>
<td>64 (45–108)</td>
<td>67 (45–108)</td>
<td>63(45–91)</td>
<td>62 (48–89)</td>
</tr>
<tr>
<td>Men</td>
<td>65 (45–108)</td>
<td>68 (45–108)</td>
<td>64 (45–91)</td>
<td>63 (48–89)</td>
</tr>
<tr>
<td>Women*</td>
<td>60 (48–79)</td>
<td>64 (48–79)</td>
<td>64 (48–79)</td>
<td>64 (48–79)</td>
</tr>
<tr>
<td>Height, cm (mean)</td>
<td>164 (140–182)</td>
<td>167 (150–182)</td>
<td>164 (147–182)</td>
<td>164 (140–179)</td>
</tr>
<tr>
<td>BMI</td>
<td>24 (18–36)</td>
<td>24 (18–36)</td>
<td>24 (18–36)</td>
<td>24 (18–36)</td>
</tr>
<tr>
<td>Men</td>
<td>23 (18–36)</td>
<td>24 (18–36)</td>
<td>24 (18–36)</td>
<td>23 (18–33)</td>
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<tr>
<td>Women*</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>28</td>
<td>38</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>Ex-smokers (%)</td>
<td>23</td>
<td>15</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Alcohol ≥ 7 drinks/week (%)</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Literate (%)</td>
<td>79</td>
<td>76</td>
<td>78</td>
<td>82</td>
</tr>
<tr>
<td>Previous harvests, N (range)</td>
<td>9 (1–38)</td>
<td>12 (1–38)</td>
<td>8 (1–34)</td>
<td>8 (1–34)</td>
</tr>
<tr>
<td>Ever used pesticides (%)a</td>
<td>89</td>
<td>95</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>At home (%)</td>
<td>40</td>
<td>55</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>At present harvest (%)</td>
<td>16</td>
<td>27</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Ever used (%)</td>
<td>52</td>
<td>64</td>
<td>66</td>
<td>58</td>
</tr>
<tr>
<td>Glycophosphate</td>
<td>76</td>
<td>84</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Paraquat</td>
<td>82</td>
<td>91</td>
<td>93</td>
<td>73</td>
</tr>
<tr>
<td>2,4-D</td>
<td>71</td>
<td>87</td>
<td>76</td>
<td>60</td>
</tr>
<tr>
<td>Organophosphates</td>
<td>76</td>
<td>84</td>
<td>85</td>
<td>66</td>
</tr>
<tr>
<td>Carbamates</td>
<td>35</td>
<td>20</td>
<td>22</td>
<td>49</td>
</tr>
<tr>
<td>Triazines</td>
<td>73</td>
<td>91</td>
<td>85</td>
<td>58</td>
</tr>
<tr>
<td>Pyrethroids</td>
<td>59</td>
<td>76</td>
<td>78</td>
<td>39</td>
</tr>
<tr>
<td>Captan</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Hypertension (N)</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes (N)</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Nephrolithiasis (N)</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Use of NSAIDs (%)</td>
<td>24</td>
<td>27</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>Use of acetaminophen (%)</td>
<td>52</td>
<td>64</td>
<td>66</td>
<td>39</td>
</tr>
<tr>
<td>Use of aspirin (%)</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Use of diuretics (%)</td>
<td>11</td>
<td>4</td>
<td>5</td>
<td>18</td>
</tr>
</tbody>
</table>

All items except body weight and height are self-reported.

* Data stratified by region not given due to few women.

a Ever used at work or at home.

b Ever used for at least one week.

globe temperature (WBGT) between 24.8 and 33.8. At noon temperature was 39–42 °C, and in the afternoon even higher (maximum 48 °C). The mean heat index (HI) was 98–111 °F, but higher if 15 °F was added, taking into account that work was performed in full sunshine (Fig. 2) (OSHA, 1999; OSHA, 2014). The average work time was about 4 hours, but varied substantially. The mean liquid intake was 0.3 L at breakfast and 3.3 L during work (mean 0.8 L per hour), and about 90% was water. The rest was mainly sweet drinks.

3.2. Pre-shift reduced renal function

Elevated pre-shift serum creatinine was common – in 20% of 168 men S-creatinine was >1.2 mg/dL, and in one of 23 women >0.9 mg/dL. In addition to a high prevalence of elevated serum creatinine, elevated serum uric acid was also common; 27% of the men had a level above 7.0 mg/dL. Twenty-three workers, all men (14%), had eGFR < 60 ml/min/1.73 m². If not temporary, this fulfills criteria for chronic kidney disease (National Kidney Foundation, 2002; KDIGO 2012). Three workers had severely reduced eGFR ( < 30 ml/min), Table 2. Workers with reduced eGFR were slightly older (mean 34 years) but the prevalence of smoking, self-reported previous disease, and use of medications or alcohol was unremarkable. None had diabetes, and only one reported hypertension. A few had proteinuria, or suspected microalbuminuria (Table 3). As expected, mean levels of serum urea nitrogen (P < 0.001), serum uric acid (P < 0.001) and urinary neutrophil gelatinase-associated lipocalin (NGAL) (P = 0.02) were higher than for other workers. Serum urea nitrogen was abnormal (>23 mg/dL) in 13 cases, and uric acid (≥7 mg/dL) in 21 cases (91%). In a backwards logistic regression model, including age, BMI, smoking, kidney stones, hypertension, use of NSAIDs, diuretics, number of previous harvests, any use of pesticides, and region, the only significant predictors of reduced eGFR were age (OR 1.09 per year, 95% CI 1.02–1.16, P = 0.008) and region (coastal versus the other two regions combined, OR 3.5, 95% CI 1.3–9.4, P = 0.01). Self-reported use of carbamate pesticides was more common among the workers with reduced eGFR (reported by 74% versus 29% among remaining workers), and a predictor in the regression model if replacing “any use of pesticides”.

3.3. Cross-shift changes in hydration and cardiovascular parameters

Some workers lost weight during the workday, but some gained weight, and the mean change during the workday was close to zero (Table 4). However, the change was positively associated with the estimated liquid intake per day (P < 0.001). In a multivariable model including region and WBGT, one extra liter of fluid increased post-shift body weight with about 0.5 kg (P = 0.008).

Urinary osmolality and urinary specific gravity (SG) increased substantially across shift, while serum osmolality did not change. The mean SG was 1.016 in pre-shift and 1.020 in post-shift samples (Fig. 3, Table S2). Post shift SG tended to be lower (P = 0.06) with increased liquid intake per hour in a multivariable model including also region, work-time, and WBGT. Serum sodium increased slightly, while potassium and chloride fell significantly (Fig. 3, Table S1).

As expected, the pulse rate was higher post-shift than pre-shift. The mean blood pressure decreased, however (P < 0.001) (Fig. 3, Table S1). In a multiple linear regression model including region, WBGT, work time and liquid intake per hour, the decrease of diastolic blood pressure was smaller at higher WBGT (P = 0.007).

Hemoglobin and hematocrit fell 3–5% (Fig. 3, Table S1). In a multivariable model including region, WBGT, work time, and...
liquid intake per hour, the decrease of hemoglobin (P=0.01) and hematocrit (P<0.001) was larger in the coastal region. High WBGT was associated with a decrease of hemoglobin (P<0.001) but an increase in hematocrit (P=0.02).

### 3.4. Cross-shift changes in biomarkers related to renal function

There were significant cross-shift increases (about 10%) in serum creatinine, urea nitrogen, and uric acid. Prevalence of elevated S-creatinine increased from 20% pre-shift to 25% post-shift, indicating a drop in GFR. Serum uric acid was elevated (> 7 mg/dL in men and > 6 mg/dL in women) pre-shift in 26% of workers, and post-shift in 43%. Urinary NGAL decreased over shift. There was a marked increase of mean urinary creatinine from 1.1 to 1.9 g/L post-shift in 43%. Urinary pH decreased as did urinary osmolality, sodium and creatinine, as well as urinary creatinine.

In a multivariable model including region, WBGT, liquid intake per hour, and work-time into account. There was also a significant effect of region.

The increase in S-creatinine was significantly larger (P<0.001) in the 23 workers with reduced eGFR in a multivariable model taking region, WBGT, liquid intake per hour, and work-time into account. This was also the case for the increase in serum uric acid (P=0.009), but not for serum urea nitrogen, which was essentially unchanged, while it increased for the other workers (P=0.03). Workers with reduced eGFR had lower urine specific gravity and osmolality than the other workers pre-shift (P=0.006) and post-shift (P<0.001). They had also lower urinary pH pre-shift (P=0.01) and post-shift (P=0.009).

If sex was added to models for cross-shift changes of biomarkers, results were similar (data not shown). The cross-shift decrease of systolic blood pressure and urinary pH was, however, larger among women.

### Table 2

Pre-shift serum creatinine and estimated glomerular filtration rate (eGFR) based on the CKD–EPI equation (Levey 2009).

<table>
<thead>
<tr>
<th>S-creatinine (mg/dL)</th>
<th>All (N=55)</th>
<th>Higher alt. (N=23)</th>
<th>Medium alt. (N=41)</th>
<th>Coast (N=93)</th>
<th>P-value difference between regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.07 (0.6–4.1)</td>
<td></td>
<td>1.09 (0.62–3.9)</td>
<td>0.88 (0.62–2.26)</td>
<td>1.13 (0.65–4.11)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### Table 3


### Table 4

Table 4

Work conditions, fluid intake, and cross-shift changes in body weight, pulse rate, and blood pressure (Systolic—SBP, Diastolic—DBP) over a work-day in 189 sugarcane workers in three different sugarcane fields. Mean (range) or number (N) is given. Temperature data are based on measurements over 2 work-days in the high altitude region, 2 days in the medium altitude region, and 3 days in the coastal region.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Higher alt. (N=55)</th>
<th>Medium alt. (N=41)</th>
<th>Coast (N=93)</th>
<th>P-value change overall</th>
<th>P-value difference between regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work hours (h)</td>
<td>4.13 (1.4–10.7)</td>
<td>6.1 (1.4–10.7)</td>
<td>2.8 (1.4–9.1)</td>
<td>3.7 (2.1–9.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cane cut (tonnes/h)</td>
<td>0.9 (0.1–2.0)</td>
<td>0.8 (0.2–1.9)</td>
<td>1.2 (0.3–2.5)</td>
<td>0.8 (0.1–1.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mean temperature°C</td>
<td>34.2</td>
<td>33.7</td>
<td>35.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean WBGT °C</td>
<td>25.2</td>
<td>27.0</td>
<td>28.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Heat Index°C</td>
<td>98</td>
<td>102</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid intake total (L)d</td>
<td>3.6 (0.25–10)</td>
<td>4.8 (1.2–10)</td>
<td>2.5 (0.3–5.1)</td>
<td>3.3 (0.25–6.8)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>3.1 (0–9)</td>
<td>4.2 (0.25–9)</td>
<td>2.2 (0.2–4.4)</td>
<td>2.9 (0–6.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Sweet drinks</td>
<td>0.4 (0–15)</td>
<td>0.5 (0–1.5)</td>
<td>0.2 (0–0.9)</td>
<td>0.4 (0–1.3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Liquid intake, L/hour</td>
<td>0.8 (0–2.0)</td>
<td>0.7 (0.3–1.2)</td>
<td>0.8 (0–1.4)</td>
<td>0.9 (0.1–2.0)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Chewing sugarcane (N)</td>
<td>28</td>
<td>14</td>
<td>10</td>
<td>4</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Body weight start (kg)</td>
<td>64.1(44.4–108)</td>
<td>67.3 (45.1–108)</td>
<td>64.6 (45.4–90.8)</td>
<td>62.0 (38.1–89)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Weight change (kg)</td>
<td>0.0 (–2.5 to 2.3)</td>
<td>0.1 (–1.4 to 1.8)</td>
<td>–0.7 (–2.5 to 0.5)</td>
<td>0.2 (–2.5 to 2.1)</td>
<td>0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulse rate Pre</td>
<td>67 (40–107)</td>
<td>65 (42–97)</td>
<td>70 (49–100)</td>
<td>67 (40–107)</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Pulse rate change</td>
<td>17 (–25 to 54)</td>
<td>20 (–9 to 54)</td>
<td>14 (–25 to 45)</td>
<td>16 (–14 to 52)</td>
<td>&lt;0.001</td>
<td>0.07</td>
</tr>
<tr>
<td>SBP Pre</td>
<td>124 (93–169)</td>
<td>120 (95–160)</td>
<td>116 (81–133)</td>
<td>120 (97–169)</td>
<td>0.03</td>
<td></td>
</tr>
<tr>
<td>SBP change</td>
<td>–8 (–42 to 35)</td>
<td>–5 (–32 to 22)</td>
<td>–10 (–35 to 17)</td>
<td>–9 (–42 to 35)</td>
<td>&lt;0.001</td>
<td>0.06</td>
</tr>
<tr>
<td>DBP Pre</td>
<td>70 (41–99)</td>
<td>68 (45–95)</td>
<td>70 (41–98)</td>
<td>72 (52–99)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>DBP change</td>
<td>–5 (–32 to 57)</td>
<td>–4 (–32 to 16)</td>
<td>–2 (–24 to 57)</td>
<td>–6 (–29 to 16)</td>
<td>&lt;0.001</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Between 6 AM and noon.

According to local laws 3 degrees should be added to these values if work was performed in full clothes.

According to OSHA rules 15 °F should be added to these values when work is performed in the sun.

*From breakfast at home until end of work. Includes 0.3 L at breakfast and 3.3 L at work (means).

*Most of these workers had lunch at the work-place.

3.5. Other biomarkers

None of the workers showed cholinesterase inhibition before or after the work shift (data not shown), which was expected since they did not use organophosphates or carbamates on that day. Liver aminotransferase enzymes showed mainly normal levels. Levels of serum CPK (only a subgroup of 30 workers) were normal with no significant cross-shift change.

4. Discussion

This study of 189 sugarcane cutters from El Salvador showed a high prevalence of reduced kidney function. The pre-shift eGFR was reduced (<60 mL/min) in 14% of male workers. Substantial cross-shift changes were noted for blood pressure as well as for kidney-related serum and urine biomarkers involved in maintaining water and electrolyte balance, and for serum uric acid. The association between the cross-shift increase in serum creatinine and temperature and liquid intake provides some empirical support to the hypothesis that kidney damage in MeN is caused by recurrent dehydration and strenuous work in a hot and humid environment. In addition, serum uric acid levels were much higher than expected (mean 6.5 mg/dL; higher than in general population).

The prevalence of reduced eGFR (14% in males) is consistent with findings in population-based cross-sectional studies in coastal Nicaragua and El Salvador (Torres et al., 2010; Sanoff et al., 2010; O’Donnell et al., 2011; Orantes et al., 2011; Peraza et al., 2012; Herrera et al., 2014), except for one study with a prevalence of 40% in men 20-49 years (Raines et al., 2014). The present study was performed exclusively in active sugarcane workers. Therefore one might expect a higher prevalence of reduced eGFR, but we included only individuals aged <50 years, and healthy enough to work as a cane cutter. In a study of cane cutters in Nicaragua at late harvest, only 3/54 (6%) had reduced eGFR, but in that study workers with elevated S-creatinine were not hired at start of harvest (Laws et al., 2015).

Age, male sex, and coastal region (where temperature and humidity is higher) were risk factors for reduced eGFR, in agreement with previous studies. Cases of reduced eGFR occurred, however, also at somewhat higher altitudes (Table 3), and could not be explained by well-known risk factors such as diabetes, hypertension, or nephrotoxic medications. Previous use of carbamate insecticides was more common among the 23 workers with reduced eGFR, but we had no a priori hypothesis regarding this specific chemical group of pesticides. It should, however, be examined further. Interestingly, elevated serum uric acid levels were very common, even more common than in patients starting kidney replacement therapy (Suliman et al., 2006).

Work as a sugarcane cutter is hard and repetitive, particularly using a machete, and walking carrying the cut cane. Short breaks are taken, but still under the sun. It is likely that part of the work, engaging arms to a large extent, will be anaerobic, resulting in increased lactate formation (Mc Ardle et al., 1991). Although the results showed some indications towards stronger effects in the coastal region, the differences were smaller than we had anticipated. The reason for this may be that within a group of workers from a specific region there are large differences in work load, water intake, and individual factors. In addition, as shown in Table 4, although the WBGT tended to be lower in the highest altitude region, the mean number of work hours was longer in this region.

The mean temperatures and WBGT were very high already in the morning. According to the US OSHA, there is need for rest about 50% of the time when WBGT exceeds 28 °C, and 75% of time when it exceeds 30 °C, to avoid increased core body temperature (OSHA, 1999). Workers did not take such breaks. If full sunshine is taken into account, the mean HI was 110–125 °F (Fig. 2), which requires aggressive protective measures (OSHA, 1999; OSHA, 2014). At these conditions the only way to counteract heat production and maintain core body temperature is by evaporation.
Fig. 3. A-C Cross-shift changes in selected outcomes in 189 sugarcane workers examined before and immediately after work. The boxes depict medians and 25th and 75th percentiles, and outliers are shown. All changes except for body weight and serum osmolality are statistically significant (P < 0.001).
The mean liquid intake (0.8 L per hour of work) seemed to be enough to maintain body weight and serum osmolality (Table 4, Table S1), but only at expense of strong demands on renal re-absorption of water by the kidney, and only for about half of the workers. Considering the strong cross-shift effects on renal physiology and the significant association between change in body weight and liquid intake, our interpretation is that liquid intake should be higher than 0.8 L per hour under these work conditions. Sweating during running typically results in loss of 0.5–2 L per hour, depending on speed and weather conditions (McArdle et al., 1991; Kratz et al., 2002; Junglee et al., 2013). In many workers part of the water intake occurred at the end of the work-shift, while ideally frequent water intake should be ascertained during work or breaks. Thus there may well have been some loss of body weight during work for most workers. Nevertheless, one third of workers lost > 0.5 kg of body weight, and showed also other signs of dehydration (Table 5). High water intake may, however, also require replacement of salts, in order to avoid hyponatremia.

Work in a hot environment will redistribute blood flow to muscles, and to skin in order to increase heat loss. This will decrease blood flow to visceral organs such as intestines and the kidneys. Hard work, even in normal temperature, will reduce renal blood flow by about 50% (Astrand et al., 2003). Sweating will cause loss of water, sodium and chloride. Together with redistribution of blood flow, this will cause a decrease in central blood volume, which we interpret as the cause of the decrease in post-shift blood pressure (Table 4). Since work conditions favored dehydration, we had expected hemococoncentration with increased hematocrit and hemoglobin, but found the opposite (Fig. 3, Table S2). Hemococoncentration occurs in parallel to loss of body weight during exercise in a hot environment, but hematocrit returns rapidly at recovery, also without hydration (Harrison et al., 1975). In these workers, who had access to water, there was probably an influx of interstitial fluid to plasma after work, as a physiologic response to the vasodilation in skeletal muscles and skin.

Loss of water by sweating and decrease of central blood volume will activate the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), resulting in release of the antidiuretic hormone (vasopressin) and aldosterone. This causes a strong increase of renal tubular reabsorption of water, sodium, and urea, as indicated by the significant increase in U-osmolality, U-SG, and U-creatinine (Fig. 3, Table S2). The aldosterone effect saves sodium, as shown by the decrease in urinary sodium excretion rate (lower post-shift creatinine-adjusted U-Na). Aldosterone also increases the excretion of potassium (decreased S-K, Fig. 3). It is likely that the loss of sodium by sweating was not balanced by the decrease in urinary sodium, and the fact that serum sodium remained unchanged may be due to influx of sodium from extracellular fluid.

The increase (about 10%) in serum levels of creatinine, urea nitrogen, and uric acid is probably an effect of reduced GFR during work (due to decreased renal blood flow, and reduced filtration pressure). Increased breakdown of muscle creatine and purine could also contribute to this. The fall of serum glucose is expected due to glucose consumption at prolonged muscular effort.

We have found only one previous published study examining cross-shift changes in sugarcane cutters; in a small study of 27 cane cutters in Brazil, all had normal pre-shift S-creatinine, which increased by 0.2 mg/dL over an 8 h shift, in agreement with our results (Paula Santos et al., 2014).

The high prevalence of elevated serum uric acid (26% pre-shift and 43% post-shift) is remarkable. The effect of aldosterone and the lactate formation decrease urinary pH (Fig. 3, Table S2). Interestingly, urate crystals were found in a relatively large fraction of workers–pre-shift as well as post-shift. Concentration and acidification of urine in combination with increased serum levels of urate, may increase formation of urate crystals, a condition which has recently been proposed (Roncal-Jimenez, submitted manuscript) as a causative factor in MeN.

The present study provides the first detailed data showing the extent of heat stress in sugarcane workers in a region with high prevalence of MeN. The concentrated post-shift urine suggests a repeated heavy load on renal tubular reabsorption. This may be compatible with histopathological findings of tubular atrophy and interstitial fibrosis in cases of MeN (Wijkstrom et al., 2013; Lopez-Marin et al. 2014). The redistribution of blood to muscles and skin indicates that renal blood flow is much reduced during work, as also supported by cross-shift increase of serum creatinine and urea nitrogen, indicating reduced GFR during work. This may be one factor behind glomerulosclerosis found in MeN kidney biopsies (Wijkstrom et al., 2013; Lopez-Marin et al., 2014). Another factor could be the increase of serum uric acid; animal studies have shown that hyperuricemia can cause renal arteriolar constriction, and eventually glomerular hypertension (Kang et al., 2002; Sanchez-Lozada et al., 2005). Acidification of urine, and relatively high prevalence of urate crystals in the sediments, support the hypothesis that urate microcrystals could be a causative factor in MeN. The finding that self-reported previous use of carbanates was more common among cases with reduced eGFR should be
addressed in larger studies of MeN.

The detailed measurements of temperature, and the comprehensive physiological data and biomarkers examined before and after a work-shift make the present study unique. Cutting squads and workers were randomly selected, and no pre-employment screening of kidney function is performed in this area, which increases the validity. Interview data on previous work, medications, and liquid intake on the workday were detailed. The study also has several limitations. It would have been an advantage to examine cross-shift changes also in a control group working in hot climate with low physical work load, or a group with similar tasks but working in a less hot climate. The pre- and post-shift sampling was only performed on one day per worker. It is likely that the workers drank more than they usually do, since they were aware that temperature and water intake was an important part of the study. True serum osmolality may have been higher due to effects of freezing and thawing of samples (Bohnen et al., 1992), but the cross-shift change should be unbiased. Other limitations include the semi-quantitative measurements of urinary albumin, and the absence of more detailed data on the timing of use of medications (ever used for > one week). We used the CKD-EPI equation which is preferable at near normal GFR (Tent et al., 2010; Murata et al., 2011), and creatinine concentrations were calibrated against creatinine determined with isotope dilution mass spectrometry. Regarding external validity it should be noted that work conditions may differ between countries, and even between mills within the same country.

Given that the main causal hypothesis is that repeated high-intensity work in a hot environment causes irreversible kidney damage, the high WBGT and the indications of a decrease of GFR during work suggest that work practices must be improved with more frequent breaks, access to shade during breaks, larger intake of water, and probably also salt. The mean intake of 0.8 L/h in the present study was enough for maintaining body weight, but not to protect the kidneys from a heavy load on tubular re-absorption and from reduced glomerular filtration.

This study suggests that workers with pre-shift reduced eGFR seem to be more sensitive to further reduction of GFR, as their serum creatinine increased more across shift than it did in other workers. It is, however, desirable that the work environment should be good enough to allow workers with reduced kidney function to take part in sugarcane work, which is often the only job alternative.

In conclusion, the present study demonstrates the very hot environment for El Salvadoran sugarcane cutters, and substantial cross-shift changes indicating a heavy load on the kidney to counteract dehydration. There is a strong need for preventive measures, which may be as simple as the provision of water, rest, and shade.

Ethics review

All participants signed a written informed consent to participate in the study, which was approved by the National Committee of Ethics for Clinical Research of the Superior Council of Public Health, El Salvador.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.07.007.

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Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy


Abstract

Climate change has led to significant rise of 0.8°C–0.9°C in global mean temperature over the last century and has been linked with significant increases in the frequency and severity of heat waves (extreme heat events). Climate change has also been increasingly connected to detrimental human health. One of the consequences of climate-related extreme heat exposure is dehydration and volume loss, leading to acute mortality from exacerbations of pre-existing chronic disease, as well as from outright heat exhaustion and heat stroke. Recent studies have also shown that recurrent heat exposure with physical exertion and inadequate hydration can lead to CKD that is distinct from that caused by diabetes, hypertension, or GN. Epidemics of CKD consistent with heat stress nephropathy are now occurring across the world. Here, we describe this disease, discuss the locations where it appears to be manifesting, link it with increasing temperatures, and discuss ongoing attempts to prevent the disease. Heat stress nephropathy may represent one of the first epidemics due to global warming. Government, industry, and health policy makers in the impacted regions should place greater emphasis on occupational and community interventions.


One of the pressing challenges facing the world is the increasing impact of climate change and water shortage (driven by both climate change and population expansion) on human health and productivity. Global warming has resulted in an overall increase of about 0.8°C during the last century, and is estimated to be responsible for 75% of the extreme heat events (1–4). Heat waves typically refer to sustained temperatures of >40°C, or temperature increases of >5–6°C over the normal maximum temperature of the region, or any time temperatures reach >45°C (5–7). One of the most intuitive effects of heat waves on human health is heat stroke and death. During the summer of 2015, for example, the heat index—which takes into account both air temperature and humidity—toppled world records at 74°C (165°F) in Iran. A heat wave in Pakistan resulted in 40,000 cases of heat stroke, and another heat wave in Andhra Pradesh took 1400 lives in 1 month (8–10). Conditions will worsen, with predictions of a rise of 3–4°C in mean temperature by the end of the century (11), which could result in intermittent temperatures incompatible with outside living in some of the hottest areas of the world, such as the Middle East (12). The rise in temperature is paralleled by an increasing shortage of water, with the percentage of the world population suffering from moderate water shortage (defined as 1.0–1.7 m³ water/person per year) skyrocketing from 5% in 1800 to 50% in 2005, and with 10% of the world population currently suffering from extreme (<0.5 m³ water/person per year) water shortage (13).

While increased risk for heat stroke is an obvious manifestation of global warming, climate change affects health in many other direct and indirect ways (14,15). Dehydration secondary to heat stress (relative water loss with development of hyperosmolarity) is associated with cognitive dysfunction, hypotension, and AKI (16). Drought can reduce crop yields, which can lead to starvation, malnutrition, and act as a threat multiplier to poverty and violence, especially in regions of the world with poor governance; likewise, extreme heat waves kill heat-sensitive cereals such as wheat and rice (17–19). Alterations in water supply, with variations in precipitation, can lead to emergence of water-borne and vector-borne infectious diseases (20,21). Drying up of wells can lead to increased concentration of heavy metals and/or toxins. Furthermore, subjects who are chronically dehydrated may not excrete toxins as effectively as those who are well hydrated, leading to higher concentrations of toxins in the serum and kidney. In addition, chronic dehydration and hyperosmolarity have also been linked with increased risk for obesity, diabetes, and metabolic syndrome (22,23). Thus, a wide variety of health issues are
likely to result from climate change over the next century, emphasizing the importance for educating physicians, industry, policy makers, and the public.

Recently, an epidemic of CKD of unknown etiology has been recognized in Central America (Mesoamerican nephropathy), which has been linked with recurrent dehydration and heat stress (24–26). We and others have previously suggested, based on both experimental and epidemiologic studies, that this disease may be a type of heat stress nephropathy (HSN) and could be an example of a disease that is accelerated by global warming (27,28). If true, one might hypothesize that similar epidemics should be occurring among those working manually in other hot environments. Unfortunately, the subjects at risk are often from impoverished and neglected populations where medical care is poor, renal biopsies are rarely performed, and diagnosis is rarely confirmed. Nevertheless, there are reports of CKD of unknown etiology emerging in other regions of the world where individuals are performing strenuous manual labor under very hot conditions (29–31).

Here, we provide a brief summary of these epidemics, and evaluate the relationship to heat stress, local environmental changes (global warming and progressive water shortages), and dietary changes (increased sugar intake). Although surveillance data are limited, the populations identified as most at risk are heavy laborers with a high workload, limited access to potable water, and otherwise extreme working conditions (32–34). We propose that HSN may be a major cause of CKD, representing an overlooked disease in neglected populations in hot communities. We suggest it may also emerge as a cause of CKD in any population where subjects are exposed to heat stress.

Mesoamerican Nephropathy

Mesoamerican nephropathy was first reported in 2002 in El Salvador by one of the authors (R.G.T.) during his medical residency, when excessive numbers of individuals were presenting at Hospital Rosales in San Salvador with ESRD (35). The disease typically presents in male sugarcane workers from the Pacific coast of Central America, but has since been reported with less frequency in other occupations, including in construction workers, corn and rice farmers, cotton plantation workers, and miners (32,36–38). In the affected areas women also have an increased prevalence of CKD, although to a much lesser extent, and there is some preliminary evidence that children from these regions may also be at risk (36,39,40). Clinically, the subjects are usually discovered with an asymptomatic rise in serum creatinine, in association with low grade or absent proteinuria, occasionally with microhematuria (36,37). Mild anemia, hypokalemia, and hyperuricemia are common (41–43). Renal biopsies show interstitial fibrosis, low grade inflammation, tubular atrophy, and extensive glomerulosclerosis with signs of glomerular ischemia but only mild vascular lesions (42,44). Progression to ESRD occurs over several years and is higher in those who work more harvests (32). Since chronic renal replacement programs are rarely available in the affected regions, many thousands have died (25).

Initial concerns were that Mesoamerican nephropathy might be due to a toxin, for example, from exposure to agrochemicals (such as glyphosate), heavy metals (such as from lead, cadmium, or arsenic), or infectious agents (such as leptospirosis) (24,45,46). The theory that this was a result of direct exposure to pesticides in the fields, however, is weakened by the presence of the disease in occupations not involving farming, by reports that there is a greater risk for renal injury in the sugarcane fields among the cane cutters as opposed to the pesticide applicators, and because the frequency of the disease is lower in sugarcane cutters working at higher altitudes where it is significantly cooler than at lower altitudes, despite similar agrochemical exposure (32,36,47). Nevertheless, it remains possible that toxins, for example, could be concentrating in well water that could affect the populations as a whole. There is also minimal evidence for heavy metal poisoning, such as from lead or cadmium (29). Nonsteroidal agent use is also common among the sugarcane workers and could be an additive factor, but several studies could not identify nonsteroidal anti-inflammatory drugs as an independent risk factor for CKD in this population (32,36,48). Infections, such as leptospirosis, remain a possible cause (49) but there is minimal evidence for this disease as a primary driver of this epidemic, and certainly some manifestations of leptospirosis, such as liver involvement, are not observed.

HSN: The Cause of Mesoamerican Nephropathy?

The Pacific coast is one of the hottest regions in Central America and aligns closely with the location of the epidemic (Figure 1). As the effects of heat are compounded by humidity and other factors, heat exposure is commonly measured by the wet bulb globe temperature (WBGT), a composite index that includes air temperature, solar radiation (globe temperature), wind speed, and humidity (50). For outside workers the Occupational Safety Health Administration recommends frequent work breaks (15 minutes per hour) for a WBGT of 26°C and breaks of 45 minutes per hour for a WBGT of ≥30°C, whereas at temperatures >35°C humans cannot maintain their body temperature by usual mechanisms (sweating) for >6 hours (12,50,51).

Sugarcane workers are particularly at risk for heat stress and dehydration due to the heavy exertion, lack of shade, infrequent breaks, long work hours (in some regions), and lack of access to sufficient potable water during the workday (50,52). Sugarcane is often burned to facilitate cutting and, depending on the local policy, some sugarcane workers enter the fields the morning after the burning, where they may be exposed to additional heat from the recently burned cane. While work begins in the early morning when the temperature is relatively cooler, the WBGT often surpasses 28°C by midmorning (53). As such, many subjects show symptoms of heat stress and dehydration when in the fields (headaches, lightheadedness, and fainting), and during the work shift their systolic and diastolic BP falls, pulse rises, and urine becomes progressively concentrated and acidic due to the activation of the renin-angiotensin-aldosterone system, with a loss of hydrogen and potassium in the urine (50,54).

Evidence that heat stress and recurrent dehydration may be the cause of Mesoamerican nephropathy is emerging. Acute dehydration is generally considered to be a reversible type of kidney failure (termed ‘prerenal’) that responds to
rehydration. However, there is an interesting report of four Bantu gold miners who developed heat stroke with AKI that recovered only to later present with CKD due to chronic interstitial fibrosis (55). Experimental studies in mice have also demonstrated that recurrent daily heat exposure and dehydration can cause chronic tubulointerstitial disease with fibrosis and inflammation, similar to what is observed in renal biopsies of subjects with Mesoamerican nephropathy (56). Interestingly, renal injury is largely prevented if rehydration is given between exposure to heat/dehydration, as opposed to at the end of the day, despite equivalent amounts of water provided. This mirrors conditions in the fields where workers often only rehydrate at lunch and at the end of the workday. The mechanism has been linked with development of hyperosmolarity with activation of the vasopressin and aldose reductase/fructokinase pathway (56,57). Recurrent dehydration, for example, activates aldose reductase in the proximal tubule, converting glucose to fructose that is metabolized by fructokinase in the proximal tubule, leading to the release of oxidants that cause local tubular injury (56). Vasopressin has also been shown to accelerate experimental CKD (58,59). In turn, repeated AKI may lead to CKD (60).

Dehydration and recurrent volume depletion may also cause CKD via other mechanisms (Figure 2). For example, volume depletion can lead to hypokalemia, which causes intrarenal vasoconstriction and hypoxia, resulting in chronic tubulointerstitial injury (61). Hypokalemia is common among sugarcane workers presenting with CKD (41–43). Nevertheless, the tubular vacuolation common in hypokalemic nephropathy (61) has not been reported. Heat stress-associated labor can also result in subclinical or clinical rhabdomyolysis from low grade muscle trauma and heat, and has been shown to occur during the work shift in sugarcane workers (34). Rhabdomyolysis is a well known cause of AKI (62), and repeated exposures may lead to CKD. Finally, hyperuricemia and uricosuria associated with heat stress may lead to excessive levels of uric acid in the urine, which may also crystallize in the urine, and this has also been documented in the affected sugarcane workers (28). Indeed, many subjects complain of intermittent dysuria from the passage of sand-like material (termed chisilata in Nicaragua and mal de orín in El Salvador) due to urate crystalluria, and this is frequent in sugarcane workers and is associated with signs of dehydration (50,63,64).

Studies in Costa Rica have shown that Mesoamerican nephropathy was probably present in the 1970s in the Guanacaste province on the Pacific coast, yet the prevalence had increased almost ten-fold in men and four-fold in women by 2010 (39). During this same time, the maximum temperatures in Central America had risen by 0.8°C–1.0°C (Figures 1 and 3). While the mean rise in temperature may seem small, temperature extremes (the number of extremely hot days) increased by 30%–75% (1). During the sugarcane harvest, maximum WBGT often surpasses the 30°C limit by 10:30 a.m., especially during the late harvest of April and May, with levels >35°C being occasionally recorded (41,50). Thus, the risk for recurrent dehydration is likely greater on these hot days. Consistent with this possibility, in a study in which uric acid was measured before and after work on four different dates during a sugarcane harvest, we noted one day in which all seven worker samples available showed extremely high uric acid levels (>100 mg/dl) compared with the other dates, and this was one of the hotter days of the year (May of 2013) (65). Thus, the risk for recurrent dehydration is likely greater on these hot days. Consistent with this possibility, in a study in which uric acid was measured before and after work on four different dates during a sugarcane harvest, we noted one day in which all seven worker samples available showed extremely high uric acid levels (>100 mg/dl) compared with the other dates, and this was one of the hotter days of the year (May of 2013) (65).

We propose that Mesoamerican nephropathy is more frequent in sugarcane workers as they are working in the most extreme conditions, as noted by heat exposure and work intensity (66). Indeed, one study found that the greatest risk for Mesoamerican nephropathy in El Salvador...
was working in sugarcane fields, with the second greatest risk factor being working in areas of high mean maximum temperature (67). However, all individuals spending time in the hot external environment, or indoors without sufficient ventilation, might be at risk, potentially explaining why there is some evidence for the presence of renal injury in other occupations, in women, and possibly in children. While the rise in disease prevalence may be due, in part, to improved diagnosis and surveillance, there is likely a true rise in incidence that correlates with climate change. Inadequate hydration is also a key factor, as some subjects are afraid of drinking well water as it may contain toxins, and others drink fructose-containing sugary beverages (juices and soft drinks) that may exacerbate the renal injury (56). Laboratory rats with heat-associated dehydration show worse renal damage if they are rehydrated with sugary beverages as opposed to water (68). Finally, there may be higher risk in sugarcane workers than in the past, as the practice of burning cane prior to harvesting was enacted only in the last few decades and this has also led to an increase in the average number of tons cut by workers in a given day. These environmental and land use factors are exacerbated by greater demands placed on sugarcane cutters, as they are paid by piece. While definitive data for Central America is lacking, a study in Brazil reported that sugarcane workers are required to cut three to four times as much as they did 20 years ago (69).

Sri Lanka Nephropathy
A similar epidemic of CKD of unknown etiology is ongoing in the northern provinces of Sri Lanka (70–73). The epidemic has been increasing since the 1980s, and currently affects more than 100,000 individuals (74). The primary population affected are young to middle-aged male rice farmers, although women working in the fields are also at risk (73,74). The CKD is clinically similar to that observed in Central America, with most subjects presenting with asymptomatic elevations in serum creatinine with normal BP and minimal proteinuria, or with the individuals discovered to already be in ESRD. Biopsies show chronic tubulointerstitial disease (75).

The etiology of Sri Lanka nephropathy remains unknown. The association of the disease with drinking well water (76) has led to concerns of toxin exposure, such as from heavy metals (cadmium and arsenic) or agrochemicals (71). While an early study linked cadmium exposure with the CKD (72), more recent studies have found minimal evidence for cadmium or other heavy metal exposure, with levels in both deep and surface wells within acceptable limits (77,78). Exposure to agrochemicals, such as glyphosphate, remain possible and some studies suggest that the disease may represent an aggregate of nephrotoxins as opposed to a single entity (71). Nevertheless, concerns that the wells are contaminated may encourage farmers not to drink local water and could predispose them to increased risk for dehydration. The Northern Province is the hottest region in Sri Lanka (Figure 4). Indeed, in one study in which 100 subjects with CKD were compared with control subjects, the risk for CKD was higher in those exposed to the sun, those working for ≥6 hours, and those drinking <3 L of water per day (risk increased between fourfold and eightfold), and this was also
associated with the presence of dysuria at the end of the work day that cannot be ascribed to urinary tract infection (76). Similar to the situation in Central America, many subjects with CKD also have hyperuricemia (mean levels of 7.2 mg/dl versus 5.2 mg/dl in controls) and hypokalemia (Channa Jayasumana, personal communication).

Figure 3. | Changing temperatures in El Salvador. Mean temperatures have increased by about 0.8˚C during this period in El Salvador, which results in a significant (30%–75%) increase in the frequency of extremely hot days (>99th percentile) (image from Berkeley Earth [http://berkeleyearth.lbl.gov/regions/el-salvador], public domain).

Figure 4. | Sri Lankan nephropathy. (A) and (B) An epidemic of CKD is occurring in the dry zone of the north central region of Sri Lanka. (C) The region is exceptionally hot, with average temperatures of approximately 30˚C. While the relationship of CKD with higher average annual temperatures is evident, it is interesting that the most northern part of Sri Lanka is also hot but does not appear to be a site of the CKD epidemic. However, this is an area where little investigation has been done, and it remains possible to be a site of under-reporting. (A) and (B) courtesy of Channa Jayasumana (106). (C) is from the Centre for Climate Change Studies, Department of Meteorology, Colombo, Sri Lanka (http://www.meteo.gov.lk/index.php?option=com_content&view=article&id=13&Itemid=132&lang=en). CKDu, CKD of unknown etiology.
The Epidemics of CKD in India

An epidemic of CKD in rural farmers (of rice, coconuts, and cashews) in Andhra Pradesh, India, was first observed by one of the authors (G.T.). A study of 1500 villagers in the Prakasham district documented 27% with serum creatinine levels >1.5 mg/dl, with 60% having an eGFR of <60 ml/min per 1.73 m² (30,79). Studies based on sites where hemodialysis is present suggest even higher rates in the Nellore District to the south, and represent rates that are about tenfold higher than in other regions of India. Similar to Mesoamerican nephropathy, the disease is observed primarily in hot, rural communities in which the primary occupation is farming. Most subjects present late and renal biopsies are not done; however, when performed they show chronic tubulointerstitial disease, with many of the features suggesting a similar disease as Mesoamerican nephropathy, including an asymptomatic rise in serum creatinine with minimal proteinuria, in the absence of diabetes and hypertension. Furthermore, many of these subjects give a history of recurrent dehydration and frequent hyperuricemia (Gangadhar Taduri, personal communication). Similar to Mesoamerican nephropathy, there is also some evidence that this disease has been present for decades but has increased in recent years. Indeed, Mani reported in 1993 that chronic tubulointerstitial nephritis (diagnosed based on clinical presentation of small kidneys with no history of edema, minimal proteinuria, and an absence of diabetes and hypertension) was the most common cause of CKD in his unit in Madras, especially among the rural farmers of the area, where it constituted 40% of all cases of CKD (80).

India has experienced rising temperatures over the last century, with a mean annual rise of 0.8°C in the last 100 years (81). This has been associated with a 10.4% decrease in annual rainfall over the last century (1901–2007), with a 17.6% decrease in annual rainy days over the same period (81). Whereas traditionally, the farmers living in rural areas relied on surface water from lakes, ponds, and shallow
well as their source of drinking water, there has been a shift toward drinking ground water that in some rural areas, such as Andhra Pradesh, is becoming increasingly limited due to inferior quality and decreasing groundwater tables (82). In Andhra Pradesh, the number of heat wave days during spring has increased markedly, with one heat wave lasting 35 days (Figure 5), and this is associated with an increase in heat strokes and mortality (5). Climate projections for the 21st century also show a nationwide increase in temperature, heat waves, and heat stress-related mortality (83). The minimum temperatures have also been increasing in recent decades and are projected to increase over the Indian subcontinent (83). This reduces the nighttime cooling that is typically available, thereby increasing hydration stress, and can also reduce crop yield, especially rice.

**Other Hot Spots of CKD**

**South Asia**

Other areas with CKD of unknown etiology are slowly being recognized (Table 1). For example, there are reports of CKD epidemics in other areas of India, including Goa, some regions in central Odisha, and Akola districts in Maharashtra (Vivek Jha, personal communication). This seems consistent with increased occurrence of heat waves and decreased rainfall in these regions (5) (Figure 5). CKD of undetermined etiology is also one of the dominant causes of ESRD in Thailand, accounting for 20%–25% of causes of ESRD (84,85). CKD of unknown etiology is highest in the northeastern (Isan) region, which is one of the hottest regions in Thailand. These subjects also show signs of recurrent dehydration, with the presence of hypokalemia, hyperuricemia, acidic urine, and passage of sand-like material with dysuria similar to that observed in Central America (Amorn Premgamone, personal communication) (86,87). These observations are consistent with epidemiologic studies in Thailand linking excessive CKD with occupational heat stress (88) and hyperuricemia (89).

**North and South America**

Back to the Americas, there are similar reports of excessive CKD of unknown etiology in Mexico, in the rural region of Tierra Blanca, Veracruz (90). Tierra Blanca has the hottest climate in Veracruz State and most of the agricultural activities include sugarcane, lime, cantaloupe, papaya, rice, mango, and bananas. The National Cardiology Institute in Mexico City has been a referral center for this population, and 58 kidney transplants from this area have been done in the past 5 years. These patients are typically young men (mean age, 29 years) with no traditional risk factors for CKD. A recent analysis in this area reported that the prevalence of CKD was 15%–25% in males aged 20–39 years old, and the death certificates from CKD report 32–77 per 100,000 deaths per year, with 20% of the deaths occurring in subjects <40 years old (91). AKI has also been reported in sugarcane workers in Brazil (34), and population-based studies are being planned in Brazil to better understand the clinical and epidemiologic situation on the ground.

There have also been reports that farm workers, most of whom are migrants, may be developing acute kidney disease and CKD at higher rates than expected in the Central Valley of California (92,93). One recent study linked hospitalizations for dehydration and AKI with the onset of heat waves in the Central Valley and other hot regions in California (94). Further studies are required to better characterize the prevalence and clinical characteristics of the CKD, but it is worrisome that it may be similar to what is occurring with farmers in other hot, rural environments. Clinicians in California and Texas have also reported immigrants from Mexico and Central America with work histories and clinical characteristics of the CKD, but it is worrisome that it may be similar to what is occurring with farmers in other hot, rural environments. Clinicians in California and Texas have also reported immigrants from Mexico and Central America with work histories and clinical characteristics consistent with the profile of the disease outlined in this paper (David Sheikh-Hamad, personal communication).

### Table 1. Confirmed and suspected sites of heat stress-associated nephropathy (CKD)

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td><strong>Confirmed Sites</strong></td>
<td></td>
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<tr>
<td>Central America</td>
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<tr>
<td>Costa Rica</td>
<td>Guanacaste</td>
<td>Wesseling et al. (39)</td>
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<tr>
<td>El Salvador</td>
<td>Bajo Lempa</td>
<td>Orantes et al. (45)</td>
</tr>
<tr>
<td>Guatemala</td>
<td>Southwest Region</td>
<td>Laux et al. (105)</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>León and Chinandega</td>
<td>Torres et al. (36)</td>
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<tr>
<td>South Asia</td>
<td></td>
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<tr>
<td>India</td>
<td>Andhra Pradesh</td>
<td>Reddy and Gunasekar (79), Abraham et al. (30)</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>North Central Region</td>
<td>Jayatilake et al. (72), Jayasumana et al. (106)</td>
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<tr>
<td><strong>Possible Sites</strong></td>
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<tr>
<td>South Asia</td>
<td></td>
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<tr>
<td>India</td>
<td>Goa, Odisha, and Maharashtra</td>
<td>Rajapurkar et al. (107)</td>
</tr>
<tr>
<td></td>
<td>Northeast (Isan Region)</td>
<td>Sirirat Anutrakulchai (personal communication)</td>
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<tr>
<td>Thailand</td>
<td>Northeast (Isan Region)</td>
<td>El Minshawy et al. (108)</td>
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<tr>
<td><strong>Middle East</strong></td>
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<tr>
<td>Saudi Arabia</td>
<td>Tabuk region</td>
<td>El Minshawy et al. (96)</td>
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<tr>
<td><strong>Africa</strong></td>
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<tr>
<td>Egypt</td>
<td>El-Minia, Upper Egypt</td>
<td>Elamin et al. (109)</td>
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<tr>
<td>Sudan</td>
<td>Southern Sudan</td>
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<tr>
<td><strong>North America</strong></td>
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<tr>
<td>Mexico</td>
<td>Tierra Blanco, Veracruz</td>
<td>Mendoza-González et al. (90)</td>
</tr>
<tr>
<td>United States</td>
<td>California Central Valley</td>
<td>Moyce et al. (93)</td>
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</table>
Notably, the Migrant Clinicians Network has initiated a survey to determine if HSN may be occurring among migrant workers in the United States (95).

**Africa and the Middle East**

In northern Africa and the Middle East, ESRD has been reported to be high in rural farm workers in El Minya in Upper Egypt (27% of cases) (96,97) and in the Tabuk area of Saudi Arabia (33% of cases) (96). Further studies are needed to address the role of heat stress and dehydration in these disorders and their relation to climate change and water supplies. Less is known about the etiology of ESRD in sub-Saharan Africa, in part because of the rarity of renal biopsy and poor overall reporting (98).

**General Mechanism for CKD**

In addition, the observation that recurrent dehydration may cause CKD also suggests that chronic dehydration or intermittent hyperosmolarity may also have a role as a general risk factor for CKD of traditional causes (57). It is interesting that both low water intake and low urinary pH have recently been identified as risk factors for CKD progression, and some studies suggest that bicarbonate therapy may slow renal disease, which might act by alkalinizing the urine and reducing uric acid crystal formation (99–101).

**Possible Low Cost Treatment Opportunities**

Prevention of HSN should focus on improving hydration and worksite practices. Given that hyperuricemia and uricosuria is common, lowering uric acid may also provide a low cost treatment opportunity. There is increasing evidence that lowering uric acid in hyperuricemic subjects can slow the progression of CKD (102,103). Noticeably, allopurinol was reported to slow renal disease progression in a cohort of patients from Andhra Pradesh, of which 25%–30% had CKD from chronic tubulointerstitial disease (104). As scale and scope of this disease grows due to improved surveillance, a warming world, increased work demands, and an increasing informal labor sector that produces more precarious populations, the costs associated with treatment and loss of productivity for countries, and industry, are likely to be enormous. Prevention, early diagnosis, and cost-effective treatment are paramount.

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**Figure 6.** Worldwide annual maximum temperature changes. Change in annual maximum temperature from 1945 to 2014 (top panel) and the average annual maximum temperature during 1945–2010 (bottom panel). From the US National Oceanic and Atmospheric Administration, Earth System Research Laboratory, Boulder, Colorado (public domain). Data definition as shown in Figure 1. EQ, equator; Tmax, annual maximum temperature.
Limitations
While the epidemics of CKD in Central America, India, and Sri Lanka are associated with recurrent heat stress and dehydration, more studies need to be performed to address if this mechanism is causual and whether similar processes are occurring at other sites (Table 1). Based on temperature patterns, we predict that similar epidemics of CKD from HSN may be ongoing and potentially discoverable in the hotspot regions of Africa and the Middle East. However, it is important to recognize that toxicity from agrochemicals, heavy metals, and nonsteroidal anti-inflammatory drugs remain potential contributing factors. It is also important to recognize that reports of CKD of unknown etiology do not in themselves support the presence of HSN, but rather require epidemiologic studies investigating the role of heat stress and recurrent dehydration as risk factors. It also remains possible that some of the “epidemics” may represent improved awareness and diagnosis rather than a new epidemic. Nevertheless, temperature maximums are increasing, especially in the equatorial zone. Figure 6 shows the change in maximum temperature between 1945 and 2014, which indicates an increase in the hot spots discussed above—South India, Sri Lanka, and Central America. The temperature increase in recent decades and in the future also leads to evaporative loss of water that will compound the reduction in water availability.

Summary
CKD that is not associated with traditional risk factors appears to be increasing in rural hot communities in association with a progressive rise in worldwide temperatures. The disease is a type of chronic tubulointerstitial disease that has only recently been recognized, and we propose that it may be due to heat stress (HSN). We believe the risk for HSN has been increased as a consequence of global warming and an increase in extreme heat waves. We further suggest this disease has a disproportionate impact on vulnerable populations, i.e., agricultural workers. Warmer temperatures, coupled with decreasing precipitation, exacerbate this epidemic by reducing water supply and water quality. We recommend epidemiologic and clinical studies to document the presence of these epidemics, their magnitude, and the role of dehydration and hyperosmolarity. A coordinated effort by governments and researchers to improve surveillance must be undertaken so we may understand the scale of the epidemic. Ongoing occupational interventions, such as the Worker Health and Efficiency Program in El Salvador (https://laislafoundation.org/the-we-program-we-can-end-cdknt-video/), and actions by the government to improve worksite conditions (such as adequate breaks for rest and adequate clothing) should be continued. Improved hydration, alkalinization of the urine, and the lowering of uric acid may represent new approaches for the prevention and treatment of this type of CKD.

Acknowledgments
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Disclosures
R.J.J. has several patents and patent applications related to lowering uric acid or blocking fructose metabolism in the treatment of metabolic diseases. R.J.J. and M.A.L. are also members of a startup company, Colorado Research Partners LLC (Aurora, CO), which is trying to develop inhibitors of fructose metabolism. All other authors declare no conflicts of interest.

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J.G. and J.L. contributed equally to this work.

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Metabolic and Kidney Diseases in the Setting of Climate Change, Water Shortage, and Survival Factors

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ABSTRACT
Climate change (global warming) is leading to an increase in heat extremes and coupled with increasing water shortage, provides a perfect storm for a new era of environmental crises and potentially, new diseases. We use a comparative physiologic approach to show that one of the primary mechanisms by which animals protect themselves against water shortage is to increase fat mass as a means for providing metabolic water. Strong evidence suggests that certain hormones (vasopressin), foods (fructose), and metabolic products (uric acid) function as survival signals to help reduce water loss and store fat (which also provides a source of metabolic water). These mechanisms are intricately linked with each other and stimulated by dehydration and hyperosmolarity. Although these mechanisms were protective in the setting of low sugar and low salt intake in our past, today, the combination of diets high in fructose and salty foods, increasing temperatures, and decreasing available water places these survival signals in overdrive and may be accelerating the obesity and diabetes epidemics. The recent discovery of multiple epidemics of CKD occurring in agricultural workers in hot and humid environments may represent harbingers of the detrimental consequences of the combination of climate change and overactivation of survival pathways.


The 21st century is bringing new challenges with population expansion, a decrease in natural resources, and climate change. Mean temperatures increased by 0.8°C since 1880, with two thirds of the change occurring since 1975, and they are projected to increase by 3°C to 4°C by the end of the 21st century.1,2 Temperature extremes have also increased by 75% because of climate change.3 Continued population growth and to a lesser extent, climate change have also resulted in decreasing water resources.4,5 Today, one half of the world population suffer moderate water shortage (i.e., 1.0–1.7 m³ water per person per year), and 10% have extreme water shortage (defined as <0.5 m³ per person per year), with the primary areas affected being Africa, southern and eastern Asia, and the Middle East.4

Increasing water shortage coupled with climate change increases the risk for dehydration-associated diseases. For example, there is increasing evidence that climate change may have a role in epidemics of CKD that are occurring among workers in hot environments.6 While this latter paper focuses on the sites of these epidemics and their relationship to local temperatures and changing climate, space constraints prevented it from being able to address a more central question on the biology of water conservation and how it relates to disease. Here we review how various species protect themselves from dehydration, and we identify nutrient, hormonal and metabolic pathways triggered by hyperosmolality that link water conservation with survival. We also discuss how these pathways may predict diseases that will dominate the next millennium. Importantly, climate change, heat stress, and water shortage not only will affect kidney disease, but risk for metabolic diseases including obesity and diabetes.

HOW ANIMALS SURVIVE WATER SHORTAGE

The transition of vertebrates from sea based to land was associated with many adaptations, but some of the most important were mechanisms to conserve water, including...
ways to store water, minimize water loss, and generate water.7

Water Storage

Some terrestrial animals store water in their bladders. The water-holding frog (Cyclorana platycephala) of the Sandy Desert of Australia, for example, stores so much water that it may double its weight.8 These frogs were a favorite source of water for the Tiwi people during hot summers. Some frogs live 5 years without drinking water, which is because they utilize water stored in their bladders and also generate water during the metabolism of fat.9,10 The giant tortoise of the Galapagos Islands stores water in their urinary bladder. After rain, the tortoise voids their bladder urine (which contains urea and other waste products) and drinks copiously to refill their bladder with fresh water. When needed, the turtle reabsorbs the water through the bladder wall, while at the same time, excreting some of its wastes into it, and over time, the osmolarity of the bladder urine increases.9

Reduced Urinary Water Losses

Homer Smith6 proposed that the evolution from aquatic to terrestrial environments required efficient ways to excrete nitrogen to help minimize loss of water.10 Most aquatic animals excrete ammonia, the simplest nitrogen product, as their means for eliminating nitrogen waste products (ammoniotely). In contrast, ammonia is not an appropriate compound for nitrogen excretion by terrestrial animals, because its renal excretion requires 400 ml water per 1 gram ammonia and blood levels >0.05 mM are neurotoxic.10 Rather, urea excretion is common among land amphibians and mammals, because it is concentrated easily and with low toxicity. Most effective is excretion of uric acid (uricotely), which requires only 1/50 the amount of water as that for the excretion of ammonia. Excretion of uric acid is the principal mechanism for nitrogen excretion in birds, reptiles, and some amphibians.10 Here, the uric acid is precipitated in the cloaca, where the last water is absorbed, and then, the urate pellet is excreted.

Although ureotelic animals have obligate water loss to help excrete metabolic wastes, urinary loss is minimized by urinary concentration, a process largely driven by vasopressin (or vasotocin in lower vertebrates). Vasopressin reduces water excretion by allowing water reabsorption in the collecting ducts, but it also increases sodium and urea reabsorption. The reduction in urine excretion by vasopressin improves urinary concentration by increasing urea accumulation in the renal medulla, which aids water reabsorption.

Reducing Nonrenal Water Loss

Water loss also occurs through the skin and lungs, where it helps regulate body temperature when animals are exposed to heat. A lack of sweating can result in a marked rise in body temperature and circulatory collapse (heat shock). In contrast, excessive sweating without rehydration may result in hypernatremia and volume depletion.

Desert rodents minimize water loss by hiding during the day in burrows, where temperatures are lower and humidity is high. Lungfish coat themselves with slime to minimize water loss as they burrow and estivate in the mud. Estivating frogs (C. platycephala) form cocoons from sloughed epithelial layers of skin.11 Tree frogs decrease water loss by secreting an impermeable waxy material onto their skin.11 Lemurs estivate in tree holes to avoid sun exposure and reduce their metabolism and water needs. The dromedary camel conserves water by minimizing sweating because of a reduction in sweat glands. The camel also does not pant and has adaptations in its nose that minimize respiratory losses of water.12,13 The consequence is significant diurnal variation in body temperature (as much as 6°C), with temperatures occasionally reaching 40°C on hot days.12 To prevent dehydration, camels ingest large volumes (up to 57 L) of water at one sitting. Despite these preventive measures, camels can become severely dehydrated.14

Metabolic Water

Water is also generated during fat and glycogen metabolism. Fat is anhydrous and contains only 10% water by weight,15 but when fat is oxidized, water and carbon dioxide are released. For every gram of fat metabolized, 1.12 ml water is generated.16 Liver or muscle glycogen also generates 0.6 ml water per gram of glycogen metabolized.17 Because glycogen is water soluble, it also releases potassium and water during metabolism, accounting for an additional 3 ml water per gram of glycogen metabolized.18,19 The marked diuresis after initiation of a low-carbohydrate diet is partially because of water released during glycogen metabolism.19 Although glycogen metabolism produces metabolic water, most organisms store more fat than glycogen. Thus, fat is the major source of metabolic water for most animals.

Metabolic water is used by many animals to survive periods of water shortage. Marine whales obtain much of their water from the burning of fat.20 Although capable of ingesting seawater and excreting a urine more concentrated than seawater, whales rarely use this method for obtaining water.20 Lungfish obtain water from fat metabolism while they estivate in the mud for 1–2 years. Desert rodents, such as the sand rat (Psammomys obesus), have high body fat, which they use to generate water during times of need. Larger desert animals, such as the camel and oryx, also use metabolic water, and in the oryx, this may account for 24% of its overall water needs.21

Some obligatory water loss by the lung occurs during fat metabolism because of the need to excrete carbon dioxide that may counter the gain of water provided during fat metabolism.22 However, animals like camels have developed techniques to reduce water loss from their airways and skin.12,13

SURVIVAL MECHANISMS ASSOCIATED WITH DEHYDRATION

Because fat and glycogen act as storage for water, it is not surprising that survival mechanisms associated with starvation and water shortage have overlapping metabolic pathways. Here, we discuss some of these mechanisms.
Vasopressin: The Survival Hormone

Vasopressin is an old hormone, with its predecessor, vasotocin, appearing 700 million years ago. Although vasopressin reduces urinary water losses in response to a loss of intracellular or extracellular fluid, it has other actions that may aid water conservation. For example, vasopressin may also reduce nonrenal water loss by acting via V2 receptors in the lungs. Vasopressin also reduces fever because of antipyretic effects that reduce water loss. In frogs, vasotocin reduces water loss through the skin and stimulates water reabsorption from the bladder when frogs are exposed to dehydrating stimuli. In humans, however, the reduction of sweating in dehydrated individuals occurs via a vasopressin-independent mechanism.

Vasopressin has other survival functions (Figure 1). Acute infusion of vasopressin increases serum glucose in humans, likely by stimulating glycogenolysis and gluconeogenesis. Vasopressin stimulates glucagon release from islet cells. Vasopressin stimulates sodium reabsorption in the cortical and outer medullary collecting ducts. Vasopressin also stimulates protein synthesis, cell proliferation, and cell hypertrophy in vitro.

Vasopressin also may stimulate fat accumulation. Vasopressin blocks fat oxidation and enhances fat accumulation by blocking lipolysis in fasting animals. In fasting animals, vasopressin reduces ketosis but increases glucose levels. Vasopressin enhances insulin resistance and fatty liver accumulation in the obese Zucker rat.

Vasopressin secretion is associated with stress responses that improve chances for survival. For example, vasopressin acutely increases BP and induces vascular constriction via the V1a receptor. Vasopressin stimulates adrenocorticotropic hormone release from the anterior pituitary via the V1b receptor and catecholamine release from the adrenal medulla, where both V1a and V1b receptors are expressed. Vasopressin activates the renin-angiotensin system and stimulates aldosterone release. These stress responses are associated with vasopressin-mediated behavioral changes that include aggression, anxiety, impulsivity, and memory.

Fructose: The Survival Nutrient

The effect of vasopressin to stimulate fat accumulation (by blocking fat oxidation), increase blood glucose (via gluconeogenesis), increase BP, and stimulate stress responses is reminiscent of the effects of fructose. It is of interest that fructose, but not glucose, stimulates vasopressin release in humans. We recently showed that orally administered fructose augments circulating vasopressin levels (as determined by measuring copeptin, a validated biomarker for vasopressin) and urinary concentration in dehydrated rats. Fructose also stimulates urinary sodium reabsorption and reduces urea excretion similar to vasopressin.

Dehydration also results in endogenous fructose production because of activation of the aldose reductase-sorbitol dehydrogenase (polyol) pathway. We found that acutely dehydrated mice show a blunted vasopressin response if endogenous fructose metabolism is abolished (by using fructokinase knockout mice). These studies emphasize a strong relationship between fructose and vasopressin.

We speculate that fructose may be a primary nutrient for survival, especially under conditions of reduced food or water availability. Indeed, the administration of fructose to fasting humans increases glucose levels (likely from the metabolism of fructose itself) and reduces

Figure 1. Vasopressin, the ultimate survival hormone. Vasopressin may have originated as a survival hormone for situations where the organism suffered from either extracellular volume or intracellular volume loss. The effects of vasopressin include actions much greater than simply preventing the loss of water but also, include generating a stress response, increasing BP, stimulating protein synthesis, stimulating fat accumulation, and maintaining elevated serum glucose (insulin resistance) to provide energy to the brain. ACTH, adrenocorticotropic hormone; CNS, central nervous system; RAS, renin angiotensin system.
ketosis, amino acid–induced gluconeogenesis, urinary nitrogen (ammonia and urea) excretion, and sodium excretion. These are the same effects observed when vasopressin is given to starving animals. Thus, fructose and vasopressin may act similarly to preserve water, salt, and fat while maintaining glucose levels as a source of energy for brain function. Viewed this way, the action of vasopressin to stimulate fat accumulation provides a mechanism for not only storing water but also, providing energy during times of food or water deprivation.

Uric Acid: The Metabolic Danger Signal

As discussed earlier, birds and reptiles excrete uric acid as their primary means for excreting nitrogen to minimize water loss. Despite uric acid being a potent extracellular antioxidant, the uric acid generated during fructose metabolism stimulates hepatic fat accumulation (by blocking fat oxidation) and gluconeogenesis, increases BP, and stimulates impulsivity in laboratory animals. In rodents, uric acid potentiates the effect of fructose to stimulate hepatic fat accumulation and gluconeogenesis. These data suggest that uric acid may also be a metabolic survival factor, which is consistent with observations that serum uric acid increases with both dehydration and starvation.

Interestingly, the rise of uric acid that occurs with protein degradation and amino acid–induced gluconeogenesis is reversed with fructose in fasting humans. Likewise, although vasopressin reduces uric acid excretion in healthy subjects, in the syndrome of inappropriate antidiuretic hormone, serum uric acid is low, and urinary uric acid excretion is high. Thus, whether uric acid has a role in water handling remains unclear and deserves additional studies.

DEHYDRATION IN HUMANS

Dehydration in the Hot Environment

Humans have obligate daily water losses from the lungs (250 ml/d) and urine (350–500 ml/d). In hot conditions, water losses from sweat may increase to 3–4 L/h and 8 L over a 24-hour period. Subjects working in hot tropical environments acclimate by producing a higher sweat rate that is lower in sodium, thereby resulting in less increase in core temperature, and also, they have higher plasma volume, less oxygen utilization, and less lactate accumulation. However, this adaptation may result in greater water loss and increased risk for hyperosmolarity. To help counter water loss from sweat, subjects living in the tropics tend to have slightly higher core temperatures during the day, with a greater fall at night, showing a similar trend as that observed in camels. Dehydration develops easily in the hot environment. An increase in serum osmolarity of 10 mosM/kg occurs within 40 minutes of exercise in the heat or with water deprivation for 24 hours. The Tsimane Indians of the Amazon show evidence of dehydration in 40% of subjects, especially on days with high temperatures and strenuous physical activity, despite mean water intake of 6 L daily. Chronic recurrent dehydration is also common in sugar cane workers in Central America who work under hot and humid conditions. After dehydration occurs, mental and physical performance worsen, total sweat volume decreases, and relative water content of sweat decreases (reflected by higher sodium concentration). Energy intake also decreases, which results in a reduction in obligate osmoles required for excretion. Ultimately, confusion, seizures, and coma may develop.

Diseases Favoring by Water Shortage and Climate Change

Heat Stroke and Acute Mortality

Heat waves increase the risk for heat stroke and heat-associated mortality. In 2015, >1400 deaths occurred from heat stroke in Andhra Pradesh, India. In a case-control study performed in Arizona, the risk for heat-associated death was 3.5-fold among agricultural workers and 2.3-fold in construction workers, and it was disproportionately higher in Native American and Hispanic American men.

Kidney Stones

The risk of kidney stones is increased in subjects with low urine output because of the effect of urinary concentration to increase concentrations of poorly soluble constituents, like calcium oxalate and uric acid. There is a relationship between mean daily temperature and risk for kidney stones, especially when temperatures exceed 30°C.

CKD

Heat stress doubles the risk for developing CKD among those working in hot environments. Recently, epidemics of CKD have been reported in India, Sri Lanka, Mexico, and Central America. The CKD observed in these areas is not because of the classic causes of CKD, such as diabetes or hypertension, but rather, seems to be a type of chronic tubulointerstitial disease. Although the roles of toxins and infections have not been completely ruled out, common risk factors for each of the epidemics are hot temperatures and recurrent dehydration that can be linked with climate change.

Although acute dehydration is known to cause a transient reduction in kidney function without permanent renal damage, chronic recurrent heat–induced dehydration causes CKD in mice. The mechanism for CKD may involve hyperosmolality-induced alteration of fructose and vasopressin metabolism. The rise in serum osmolality stimulates vasopressin and increases intrarenal fructose generation via activation of the aldose reductase pathway. The metabolism of fructose within the proximal tubule results in local oxidative stress, inflammation, and uric acid generation, which induce local injury. Experiments also document a role for vasopressin in CKD. An increase in serum and urinary uric acid also occurs with heat and exercise, which increases the risk for urinary urate crystal formation.

The possibility that dehydration may be a risk factor for CKD should also be considered. Low urine output and high urine osmolality predict risk for the progression of CKD. Low intake of plain water increases the risk for CKD,
whereas intake of other beverages does not show the same effect.\textsuperscript{94} Likewise, high vasopressin levels (indicated by high plasma copeptin levels) are associated with increased risk for microalbuminuria.\textsuperscript{96,97} Currently, there is a randomized trial to determine if supplementation with water to increase urinary output to 3 L/d slows the progression of CKD.\textsuperscript{98}

\textbf{Obesity, Metabolic Syndrome, and Hypertension}

As mentioned, fructose and vasopressin show similar effects to increase fat stores and conserve water (Figure 3). This suggests that transient elevations in serum osmolarity because of either a relative water deficit or a high-sodium diet might be associated with increased risk for obesity and metabolic syndrome. Evidence supporting hyperosmolarity as a risk factor for obesity and metabolic syndrome is increasing.

First, obese subjects have elevated plasma sodium and plasma osmolarity.\textsuperscript{99} Second, plasma hypertonicity predicts the development of diabetes in subjects $>70$ years old.\textsuperscript{100} Third, subjects with metabolic syndrome and insulin resistance have elevated plasma copeptin levels.\textsuperscript{101–104} Fourth, elevated levels of plasma copeptin predict development of diabetes\textsuperscript{96,105} and obesity.\textsuperscript{96}

Although inadequate hydration and hot temperatures facilitate hyperosmolality, it could also be enhanced by a high intake of salt with a less than adequate intake of water. In this regard, low water intake predicts development of insulin resistance,\textsuperscript{106} whereas increasing water intake is associated with weight loss, at least in overweight subjects.\textsuperscript{107} High salt intake is also associated with obesity, metabolic syndrome, and diabetes\textsuperscript{108–112} and predicts these conditions independent of energy intake or intake of sugary beverages.\textsuperscript{112–114} Thus, the development of obesity is not simply because of greater intake of soft drinks consequent to salt-induced thirst, which has been suggested.\textsuperscript{115} Furthermore, subjects given a high-salt diet show reduced insulin sensitivity within 5 days.\textsuperscript{116} Conversely, hyperinsulinemia promotes distal tubular sodium retention.\textsuperscript{117}

Hyperosmolality likely increases the risk for obesity and metabolic syndrome by stimulating vasopressin (Figure 3). Indeed, water loading reduced fat content of the liver of obese Zucker rats coupled with a reduction in vasopressin levels.\textsuperscript{37} However, hyperosmolality is likely acting via another pathway as well. We recently found that mice fed a high-salt diet for 5 months develop leptin resistance, obesity, and metabolic syndrome (M.A. Lanasa \textit{et al.}, unpublished...
data). The mechanism was shown to be caused by hyperosmolarity-mediated upregulation of aldose reductase in the liver, which resulted in endogenous fructose generation via the polyol pathway. Importantly, mice unable to metabolize fructose because of genetic deletion of fructokinase were protected from developing metabolic syndrome and fatty liver, despite ingesting equal amounts of salt.

Hypertonicity also regulates BP and the immune system. Hypertonicity in mice activates a transcription factor, NF of activated T cells 5, that stimulates macrophages to sequester salt in the skin, thereby modulating BP. Salt-induced hypertonicity also activates T helper 17 lymphocytes involved in host defense.

**SUMMARY**

In summary, climate change and low water intake are increasing our risk for dehydration–associated kidney diseases, including kidney stones, heat stroke, and CKD. Hyperosmolarity, especially in a sedentary environment, may also increase the risk for obesity and diabetes. We speculate that hyperosmolarity triggers factors originally designed to aid survival by increasing fat stores and conserving water, such as vasopressin, endogenously produced fructose, and uric acid. Overactivation of these pathways may act in synergy with Western diets high in fructose-containing sugars, salt, and purine-rich foods to accelerate the obesity and diabetes epidemics (Figure 2). Similarly, recurrent dehydration and heat stress may also be playing a role in causing CKD via similar pathways.

More studies are needed to investigate the effect of climate change and water shortage on kidney disease and diabetes and especially, the role of vasopressin, fructose, and uric acid. Intervention studies to improve worksite conditions and hydration among agricultural workers in tropical communities and other at–risk groups are recommended.

Recognizing the importance of the kidney in climate change–associated disease will prepare nephrologists to face an increase in heat stress–associated kidney diseases predicted to occur in the next decades.

**ACKNOWLEDGMENTS**

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**DISCLOSURES**

R.J.J. has several patents and patent applications related to lowering uric acid or blocking fructose metabolism in the treatment of metabolic diseases. R.J.J. and M.A.L. are members of a startup
company; Colorado Research Partners LLC (Aurora, CO), that is trying to develop inhibitors of fructose metabolism. R.J.J. also has some shares with XORT Therapeutics (Calgary, AB, Canada), which is a startup company developing novel xanthine oxidase inhibitors. R.J.J. is on the Scientific Board of Amway as well.

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Lecture: Global Burden of Cancer in LMICs

Lecturer: Rosemary Rochford

Viral-associated malignancies in Africa: are viruses ‘infectious traces’ or ‘dominant drivers’?
Rosemary Rochford¹, Anne Korir² and Robert Newton³,⁴

Since the discovery of Epstein-Barr virus (EBV) the first human virus associated with cancer in 1964, the number of human malignancies associated with viruses has grown. A review of cancer incidence reveals substantial variation in the incidence of such cancers around the world. In some parts of Africa, the majority of cancers are caused by infectious agents. However, there remain huge challenges in measuring the burden of cancer, especially in sub-Saharan Africa. Despite this limitation, it is clear that viral-associated malignancies are key drivers of cancer incidence rates in Africa. Prevention is available through vaccination for some but development of vaccines for others remains an important goal.

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Introduction
In the late 1950s there was much debate as to whether viruses were capable of causing cancer in humans, but the discovery of Epstein-Barr virus (EBV) in 1964 in cells from lymphoma patients in Uganda opened the door to the realization that indeed a number of human malignancies are caused by or associated with infections. The list of viruses that the International Agency for Research on Cancer (IARC) has identified as known carcinogens includes EBV, Kaposi’s sarcoma herpesvirus (KSHV), human papillomavirus (HPV), human T cell leukemia virus (HTLV)-1, hepatitis C virus (HCV) and hepatitis B virus (HBV) [1]. While the focus of this review is on virus-associated malignancies, we would be remiss in failing to mention other infection-associated cancers. For example, the gastric bacterium Helicobacter pylori is a cause of gastric cancer and a number of parasites have also been linked to various tumors — including malaria (in conjunction with EBV) in the etiology of Burkitt lymphoma and Schistosoma haematobium as a cause of bladder cancer. And while the world moved from cancer research in Uganda to discoveries elsewhere, the burden of infection-associated malignancies remains particularly high in sub-Saharan Africa. In many settings however, it remains a significant challenge to determine the incidence of infection-associated malignancies. In this review, we will examine what is known of the incidence of such tumors in Africa, the importance of population-based cancer registries and finally, how with the growing burden of non-communicable diseases in Africa, there is an opportunity for prevention through vaccination.

Population-based cancer registries
The World Health Organization Global Status Report on non-communicable diseases (NCDs) in 2010 drew attention to the growing global burden of NCDs, particularly in low and middle income countries [2]. Its publication was followed in 2011 by a meeting of the United Nations General Assembly—only the second such meeting to focus on health (the first in 2001 was on human immunodeficiency virus infection). The resulting Political Declaration recognized the increasing impact of NCDs in low and middle income countries and reiterated an emphasis on four major contributors to NCD mortality: cancer, cardiovascular disease, diabetes and chronic respiratory disease. It went on to highlight the importance of only four major risk factors: tobacco use, physical inactivity, unhealthy diet and harmful use of alcohol. However, the report contained few data from sub-Saharan Africa and relied heavily on extrapolations from elsewhere.

The United Nations estimate that the population of Africa will rise by 50% from about one billion to 1.5 billion by 2030 and that the number of people aged 60 years or over — the age group at which cancers most commonly occur — will increase by over 90% [3]. Population based cancer registries (PBCR) provides data on cancer incidence within a defined population and is considered an essential part of the public health tool kit to develop public health policies and evaluation of interventions. PBCR covers only two percent of the African population [4]. In the most recent report from IARC to assess the burden of cancer worldwide, only 8 of the 290 cancer registries contributing data were from Africa [5]. Additional data comes from vital registration (e.g. recording of live births, death). Only two
countries in Africa (Egypt and South Africa) have any system of vital registration to measure cause-specific mortality. Furthermore, on this basis, we have only very crude estimates of cancer incidence and mortality over time [6]. In 2008, there were thought to be about 715 000 new cases of cancer in Africa and 542 000 deaths from the disease, although this is likely to be a significant under-estimate of the true burden [7]. On the basis of projections for population growth and aging alone, conservative calculations indicate that by 2030, these figures will more than double [8]. This prediction takes no account of a changing risk factor profile on the continent, with increasing urbanization and epidemiological transition, perhaps leading to yet further rises in cancer incidence and mortality [8,9]. There is an urgent need therefore to develop appropriate cancer control strategies.

However, cancer is a heterogeneous set of diseases and it has been argued that a more geographically specific approach is needed in order to develop effective cancer prevention programs [10]. Data from a number of countries in sub-Saharan Africa, highlight the importance of cancers caused by underlying infections rather than by those four NCD risk factors emphasized by the 2010 WHO report [2] and subsequent UN Declaration [11]. In Uganda for example, whilst the impact of factors associated with western lifestyles on cancer incidence trends in the capital city, Kampala, is evident, these effects may be less marked in rural areas, where the majority of Ugandans still live [10]. There are limited population-based data on cancer incidence trends in urban centers in Africa and none from rural settings. Similarly, there are few data on the prevalence of known risk factors for cancer, especially in rural populations.

Therefore, accurate data on cancer mortality and incidence are vital, not just for identifying levels of disease in populations, prioritizing activity of health services and monitoring success of cancer control initiatives, but also because an understanding of patterns of disease incidence underpins epidemiology and can provide insights into disease etiology. A classic example of the latter is the recognition by Denis Burkitt, that the geographic distribution of endemic Burkitt lymphoma (BL) in Africa coincides with that of falciparum malaria — now known to be an important co-factor in the etiology of this childhood cancer. Denis Burkitt went on a ‘tumor’ safari to identify the distribution of the cancer that now bears his name [12]. What is needed however, is to extend population based cancer registry system throughout Africa to identify the epidemiology of other virus-associated cancers, develop the tools for prevention, and to monitor and evaluate prevention efforts.

**EBV-associated malignancies**

While BL was the first cancer found to be associated with EBV, there are now a number of malignancies linked to the virus including Hodgkin’s lymphoma, nasopharyngeal carcinoma, a sub-type of gastric lymphoma, and NK/T cell lymphomas [13]. BL is found in three forms: endemic, sporadic and AIDS-associated [14]. The endemic form of BL is a pediatric cancer that occurs in regions where high levels of malaria transmission particularly in sub-Saharan Africa. The detection of EBV in BL tumors is variable with almost all of the endemic form of BL having EBV, while less than 30% of the AIDS-associated are EBV-positive and EBV is rarely detected in the sporadic form of BL [14]. Studies on the incidence of the endemic form of BL go back to the early pioneering work of Burkitt and Haddow who mapped cases of BL throughout Africa [15,16]. Subsequent studies in Uganda [17] and more recently in Kenya [18], have shown that incidence rates (IR) of BL can vary markedly even between smaller geographic regions. In Kenya, the IR of BL was found to be highest in regions where malaria transmission was also high [18]. Notably, the reported incident rate was much higher than reported [7] where only data from cancer registries in Nairobi and Eldoret were available. Both of these regions have low malaria transmission and consequently, a low risk of BL. This highlights how having data from only a regional cancer registry is likely to under-report the incidence of a particular cancer across a nation or different geographical regions. There has been some question as to whether BL incidence has declined since the widespread introduction of anti-malaria preventative such as bed nets and indoor residual spraying but there has been no definitive study to date that addresses this question.

The detection of nasopharyngeal carcinoma (NPC) in Africa was first described by the pathologist, Peter Cliffeford [19]. He reported on a case series of NPC patients seen in Nairobi, Kenya and although anecdotal, noted that there were more cases of NPC than BL [19]. The highest incidence of NPC is in Asia but the African continent has the 2nd highest incidence rates worldwide [20].

There is little if any information on the extent of EBV-linked gastric carcinomas nor NK/T cell lymphomas in African cancer registries. This could be partly due to the challenges in pathologic diagnosis [21] and the rarity of these cancers overall.

**KSHV-associated malignancies**

KSHV (also known as human herpesvirus 8, HHV8) has been identified as a causal factor in Kaposis sarcoma (KS) [22]. There is both an endemic form and an AIDS-associated form of KS [7]. The incidence of KS dramatically increased in Africa as a consequence of the HIV epidemic [7] and while control of HIV infection through introduction of anti-retroviral drugs has reduced the incidence of KS in the US and Europe [23], KS remains a significant problem in Africa [24]. Strikingly, in some
cancer registries in Africa, KS has the highest incidence of any cancer in males and 2nd highest in females [7]. Retrospective studies on the epidemiology of KS have found that there was an endemic form of KS that is not AIDS-associated that preceded the AIDS epidemic [25]. KS is also found in children in parts of sub-Saharan Africa.

Two other diseases are caused by KSHV, namely Castleman’s disease and primary effusion lymphoma [26]. Because lymphoma diagnostics are limiting in Africa [21] and cancer registries typically don’t have cancer sub-type details even if the correct pathologic diagnosis was available, it is hard to determine the frequency of these diseases in regions of Africa where KSHV seropositivity is high.

HPV-associated malignancies

In the developed world, the incidence of invasive cervical cancer has dropped dramatically due to widely implemented cancer screening protocols. In contrast, sub-Saharan Africa has the highest incidence of cervical cancer world-wide [27] with cervical cancer as either the most common or 2nd most common cancer in women in most countries in Africa reporting cancer incidence [28]. There are 12 HPV types that have been identified as carcinogenic in humans, HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 [1]. Of these, HPV16 was the most common type detected in cervical cancer cases from Africa ranging from 38.5% in a study in Mali [29] to 81.8% in Tanzania [30]. A meta-analysis of cervical cancer cases from across Africa found HPV16 most frequently detected in HPV-positive cervical cancer cases, followed by HPV18, HPV35, and HPV45 [31].

Other cancers linked to HPV, and in particular to infection with HPV16, are penile, anal, vulvar, and vaginal carcinoma but these are rare cancers [32] and there is little to no information on their incidence in Africa. Carcinoma of the oropharynx — also linked to HPV — has been increasing in the developed world but there are few studies available on the incidence of these cancers in Africa. In one case study in Senegal, the incidence of HPV-positive head and neck cancers was very low [33] suggesting that HPV is not a major contributor to head and neck cancers in Africa.

HBV-associated malignancies

Chronic infection with HBV is thought to be the primary cause of hepatocellular carcinoma (HCC) in sub-Saharan Africa [34]. Worldwide, the highest rates of liver cancer occur in sub-Saharan Africa as well as regions of the Pacific and East Asia [35]. Overall, in Africa, liver cancer is the 2nd most common diagnosed cancer in men and 3rd most common in women [36]. There are geographical differences in the incidence of liver cancer within sub-Saharan Africa, where in the Gambia, over 60% of all cancers were liver cancer [37] whilst in Nairobi, Kenya, liver cancer is only the 6th most common cancer [38]. The data from the Gambia is from a long-standing PBCR and represents the first attempt to evaluate whether HBV vaccination is having an effect on liver cancer incidence [37]. While no decrease in incidence rates of adult HCC has yet been observed in the Gambia since the introduction of an HBV vaccination campaign, this study highlights the importance of having strong population based cancer registry data to evaluate cancer control programs.

HCV-associated malignancies

Chronic infection with hepatitis C virus (HCV) is linked hepatocellular carcinoma. The prevalence of HCV in Africa ranges between low levels (<2% in East Africa), moderate levels (2.0–2.8% in most of Africa) to high levels (3.6% seroprevalence in Northern Africa to 6% in West Africa) [39]. The incidence of HCV-associated HCC is lower than for HBV-associated HCC but remains an important contributor to infection-associated malignancies in Africa [34].

HCV is also associated with non-Hodgkin lymphoma (NHL) [40,41]. The incidence of HCV-associated NHL is higher in regions where the incidence of underlying HCV infection is high and likely represents up to 10% of NHL cases [42].

HTLV-1-associated malignancies

HTLV-1 causes adult T cell leukemia (ATL). The cancer was first described in Japan in the 1970s [43] with the identification of the virus soon after [44]. The epidemiology of ATL varies throughout different countries that are endemic for HTLV-1 infection [45]. There have been a few studies of HTLV-1 seroprevalence in Africa with ranges from 0.6% in Morocco [46], greater than 2% of the adult population in Gabon and Malawi [47,48] and a much higher seroprevalence of 5.2% in Guinea-Bissau [49]. This level of endemicity is comparable to Japan [50], where the risk of developing ATL in HTLV-1 carriers ranges between 4.5% to 7.3% for men, and up to 3.8% for women [45]. There are no estimates available for the risk of ATL in the HTLV-1 endemic regions of Africa. Although there are reports of HTLV-1 positive lymphomas, these are from very limited number of case studies [51] so it is hard to quantify the burden of ATL within any given HTLV-1 endemic region. A major challenge with knowing whether ATL represents an infectious trace in the African cancer registries, is that typically, leukemias are not sub-classified in the registries and are often combined with the lymphomas. As with other viral-associated lymphomas, the lack of accurate pathologic diagnosis also likely leads to under-reporting of cases.

HIV-associated malignancies

A discussion of infectious associated cancers in Africa must include a mention of the often substantial effect of the HIV epidemic on cancer incidence. In particular,
KS has exploded in incidence in the era of HIV [52]. Other HIV-associated cancers include cervical cancer (much the commonest cancer among women in Africa) [27], lymphomas [64], and conjunctival squamous cell carcinoma, which is also known to have increased in incidence very substantially in recent years [53]. In 2013, 4.7% of the population in sub-Saharan Africa was infected with HIV [54]. Although there has been great strides in providing anti-retroviral treatment for HIV throughout the continent, it is estimated that 61% of the HIV-infected population have no access to drugs [54]. Thus, the impact of HIV infection on increasing the incidence of these cancers in Africa cannot be underestimated [55,56].

A challenge in linking any given cancer to HIV infection is that HIV serostatus is rarely collected in African cancer registries. One approach to address this was developed using a clinical ‘strength-of-evidence’ approach during cancer registration to identify HIV-associated malignancies in Kenya [57]. Using this approach, three-times more HIV-associated cases were identified than when using HIV-serology alone as an indicator. This suggests that the number of HIV-associated malignancies in sub-Saharan Africa is significantly under-reported.

Opportunities for vaccination to prevent cancer
There are two oncogenic viruses that have effective licensed vaccines, HBV and HPV. HBV vaccines are now part of the Expanded Program in Immunization sponsored by the World Health Organization. The coverage of the African infants receiving a birth dose of the HBV vaccine was only 13% [58]. In South Africa following the introduction of the HBV vaccine in 1995, the incidence of prevalence of chronic HBV carriage decreased along with a decreased incidence of pediatric hepatocellular carcinoma [59] highlighting the value of HBV vaccination in cancer prevention.

The first vaccines targeting the most common HPV types, HPV16 and 18, were licensed in the US in 2006. Given the high prevalence of HPV16 and HPV18 positive cervical carcinomas, this suggests that implementation of HPV vaccines will be able to prevent the majority of cervical cancer cases in Africa. However, while the implementation of HPV vaccines into national cancer vaccination campaigns has occurred in many developed countries, it is only recently with the inclusion of HPV vaccines in the Global Alliance for Vaccines and Immunization (GAVI) immunization package for eligible countries that here has been the introduction of the vaccines in Rwanda and Uganda. Seven additional African countries have implemented HPV vaccine demonstration programs. Given the high burden of mortality associated with cervical cancer in Africa, widespread use of the HPV vaccines is urgently needed.

Efforts to develop a vaccine for KSHV have been limited [60]. In contrast, there has been more attention to developing an EBV vaccine [61]. However, there is only one EBV vaccine that passed Phase 2 trials [62] but no further development has been reported. An interesting alternative is to develop therapeutic vaccines for that induce immunity to EBV proteins in cancer patients [63]. A phase 1 trial of this approach was successful [63] and the potential for targeted vaccination of EBV-associated cancer patients represents an exciting alternative.

Summary
Because of the limitations in cancer registry capacity in Africa, there is a lack of data to determine the true burden of infection-associated cancers across this continent and the data available is likely to under represent the true burden of infectious-associated cancer. Nonetheless, KS, liver cancer and cervical cancers dominate the landscape of cancers on the African continent in contrast to the distribution of these cancers in other regions of the world. The opportunity for cancer prevention by vaccination has been revealed by the widespread use of HBV vaccination. Challenges remain to have widespread distribution of HPV vaccines in Africa.

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References
Viruses and cancer


Lecture: Cardiovascular Disease in Africa and Beyond

Lecturer: Ed Havranek

**BACKGROUND**

Global deaths from cardiovascular disease are increasing as a result of population growth, the aging of populations, and epidemiologic changes in disease. Disentangling the effects of these three drivers on trends in mortality is important for planning the future of the health care system and benchmarking progress toward the reduction of cardiovascular disease.

**METHODS**

We used mortality data from the Global Burden of Disease Study 2013, which includes data on 188 countries grouped into 21 world regions. We developed three counterfactual scenarios to represent the principal drivers of change in cardiovascular deaths (population growth alone, population growth and aging, and epidemiologic changes in disease) from 1990 to 2013. Secular trends and correlations with changes in national income were examined.

**RESULTS**

Global deaths from cardiovascular disease increased by 41% between 1990 and 2013 despite a 39% decrease in age-specific death rates; this increase was driven by a 55% increase in mortality due to the aging of populations and a 25% increase due to population growth. The relative contributions of these drivers varied by region; only in Central Europe and Western Europe did the annual number of deaths from cardiovascular disease actually decline. Change in gross domestic product per capita was correlated with change in age-specific death rates only among upper-middle income countries, and this correlation was weak; there was no significant correlation elsewhere.

**CONCLUSIONS**

The aging and growth of the population resulted in an increase in global cardiovascular deaths between 1990 and 2013, despite a decrease in age-specific death rates in most regions. Only Central and Western Europe had gains in cardiovascular health that were sufficient to offset these demographic forces. (Funded by the Bill and Melinda Gates Foundation and others.)
Globally, deaths from cardiovascular and circulatory diseases are increasing.¹ This increase represents the combined effect of population growth, the aging of populations, and epidemiologic changes in cardiovascular disease. It is important to disentangle these drivers of the observed trends in global mortality for a number of reasons. First, regional and national investments in cardiovascular health can target only the epidemiologic causes of cardiovascular disease. Second, understanding the roles and relative magnitude of these demographic and epidemiologic trends is important in planning for the health care system and in developing policy. Third, the effects of the aging and growth of the population should be excluded when progress toward the goal set by the United Nations for a 25% reduction in premature mortality due to cardiovascular disease by the year 2025 is benchmarked.²³

The Global Burden of Disease Study 2013 (GBD 2013) used standardized methods to estimate age-specific cardiovascular mortality in 188 countries from 1990 through 2013, allowing comparisons over time and across regions. To better understand the observed trends in mortality in the context of large demographic shifts, we examined separately the contribution of three causes of change in the number of cardiovascular deaths: change in population size, aging of the population, and changes in age-specific cardiovascular death rates. Because epidemiologic changes in cardiovascular disease in developing nations have been attributed to the economic growth of those nations, we also examined the relationship between changes in cardiovascular mortality due to age-specific death rates and changes in gross domestic product (GDP) per capita for each country.⁴

METHODS

ESTIMATION OF MORTALITY

The methods used in GBD 2013 have been reported elsewhere,⁵ and relevant aspects are summarized in the Supplementary Appendix, available with the full text of this article at NEJM.org. In brief, the study included 188 countries, which were grouped into 21 globally exhaustive regions for analysis (Fig. 1, and Table S1 in the Supplementary Appendix). We defined 240 causes of death, including 10 distinct cardiovascular causes of death and a combined category for less common cardiovascular and circulatory causes of death (Table 1). All available data on global mortality were collected, including death records from vital registration, sample registration, and verbal autopsy, burial and mortuary data, data on in-hospital deaths, police reports, national census data, and relevant surveys. (Vital registration systems seek to collect all death records, whereas sample registration systems collect death records from a representative subsample of a population.) Nonspecific conditions reported as an underlying cause of death were redistributed with the use of statistical methods or with causes assigned by consensus among experts.⁷ Different versions of codes from the international systems for the classification of disease were mapped to a uniform system. We used ensemble models to estimate cause-specific mortality according to age and sex across all countries in the study; estimates were based on the data collected on mortality and a large set of country-level covariates.⁸ Out-of-sample validity testing was performed for each cause-specific model, and we determined uncertainty intervals by taking 1000 draws from the posterior distribution of ensemble models, with point estimates taken as the median value. An algorithm was used to adjust these estimates for consistency with global estimates of all-cause mortality.

DETERMINATION OF DRIVERS OF CARDIOVASCULAR MORTALITY

To analyze the drivers of cardiovascular mortality, we used age-specific, sex-specific, and cause-specific mortality data from GBD 2013. We determined the total number of cardiovascular deaths by summing the numbers of deaths for each specific cardiovascular cause in each region. We decomposed the drivers of change in the number of cardiovascular deaths from 1990 to 2013 into three explanatory components for each country: growth in the total population, the change in the population structure with regard to age and sex, and the change in the age-, sex-, and cause-specific rates of death. We computed two different numbers for death using a set of simple counterfactual scenarios. First, we calculated a scenario for population growth in which the number of deaths was equal...
to the number expected in 2013 if the total population increased as actually observed from 1990 to 2013 but the age- and sex-specific population structure and death rates remained as they were in 1990. Second, we calculated a scenario for population growth and aging in which the number of deaths was equal to the number expected in 2013 using 2013 age- and sex-specific population numbers but holding constant 1990 age- and sex-specific rates of death. The difference between deaths observed in 1990 and those estimated for 2013 through the population-growth scenario is the change in the number of deaths due to population growth alone. The difference between the population-growth scenario and the scenario for population growth and aging is the change due to population aging alone. The difference between the scenario for population growth and aging and the number of deaths actually observed in 2013 is the epidemiologic change in the age-, sex-, and cause-specific death rates. We repeated our analysis 1000 times for each age-, sex-, and country-specific rate of death using the complete set of 1000 draws from the results of ensemble models and report both the mean and 95% uncertainty interval of the resulting distribution.

Each difference is presented as a change in the absolute number of cardiovascular deaths and the percentage change, with 1990 as the reference year. For example, there were 349,153 cardiovascular deaths in the high-income Asia–Pacific region in 1990. In 2013, there were 487,170 cardiovascular deaths, which is less than the 910,042 that would have been expected if 1990 death rates had remained constant, given the population size and the age structure in that region in 2013. We report this difference as a net decrease of 121% in the age- and sex-specific death rates (422,872 fewer cardiovascular deaths than expected divided by 349,153 cardiovascular deaths observed in 1990). We used Pearson’s and Spearman’s correlation coefficients to examine the relationship between...
The change in GDP per capita and the change in age-specific death rates within World Bank income strata. GDP was obtained from a complete time series of country-specific GDP per capita, expressed in 2005 international dollars, for the years 1990 and 2013.9

Table 1. Observed and Counterfactual Changes in Global Deaths Due to Cardiovascular Diseases, 1990–2013.*

<table>
<thead>
<tr>
<th>Disease</th>
<th>Deaths in 1990</th>
<th>Deaths in 2013</th>
<th>Percentage Change, 1990–2013</th>
<th>Percentage Change from 1990 Due to Age Structure, 1990 Death Rates</th>
<th>Percentage Change from 1990 Due to Population Growth</th>
<th>Percentage Change from 1990 Due to Population Aging</th>
<th>Percentage Change from 1990 Due to Change in Age-Specific Death Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>5,737,483</td>
<td>8,139,852</td>
<td>41.7</td>
<td>7,089,534</td>
<td>23.6</td>
<td>10,104,606</td>
<td>52.5</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>2,182,865</td>
<td>3,272,924</td>
<td>50.2</td>
<td>2,652,984</td>
<td>21.6</td>
<td>4,009,559</td>
<td>62.1</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>2,401,931</td>
<td>3,173,951</td>
<td>30.7</td>
<td>3,046,620</td>
<td>28.6</td>
<td>4,475,353</td>
<td>59.5</td>
</tr>
<tr>
<td>Hypertensive heart disease</td>
<td>622,148</td>
<td>1,068,585</td>
<td>74.1</td>
<td>804,870</td>
<td>29.5</td>
<td>1,201,735</td>
<td>63.6</td>
</tr>
<tr>
<td>Cardiomyopathy and myocarditis</td>
<td>293,896</td>
<td>443,297</td>
<td>51.4</td>
<td>373,574</td>
<td>27.4</td>
<td>486,334</td>
<td>38.4</td>
</tr>
<tr>
<td>Rheumatic heart disease</td>
<td>373,493</td>
<td>275,054</td>
<td>−26.5</td>
<td>493,302</td>
<td>31.8</td>
<td>653,518</td>
<td>42.8</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>99,644</td>
<td>151,493</td>
<td>52.1</td>
<td>133,978</td>
<td>34.5</td>
<td>172,230</td>
<td>38.3</td>
</tr>
<tr>
<td>Atrial fibrillation and flutter</td>
<td>28,916</td>
<td>112,209</td>
<td>288.1</td>
<td>39,136</td>
<td>35.4</td>
<td>52,484</td>
<td>46.2</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>45,053</td>
<td>65,036</td>
<td>46.3</td>
<td>64,331</td>
<td>42.2</td>
<td>78,714</td>
<td>32.0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>15,875</td>
<td>40,492</td>
<td>155.3</td>
<td>24,406</td>
<td>53.7</td>
<td>27,386</td>
<td>18.7</td>
</tr>
<tr>
<td>Other cardiovascular and circulatory diseases</td>
<td>478,261</td>
<td>554,588</td>
<td>15.2</td>
<td>638,716</td>
<td>33.7</td>
<td>852,357</td>
<td>44.9</td>
</tr>
<tr>
<td>Total</td>
<td>12,279,565</td>
<td>17,297,480</td>
<td>40.8</td>
<td>15,361,450</td>
<td>25.1</td>
<td>22,114,276</td>
<td>55.0</td>
</tr>
</tbody>
</table>

* Decomposition of the observed number of cardiovascular deaths in 1990 and 2013 was used to calculate the contribution of three explanatory components: growth in the population, aging of the population, and change in the age-, sex-, and cause-specific rate of death. The age-, sex-, and cause-specific rate of death, which in this study is referred to as epidemiologic change, includes all changes in mortality that are not explained by demographic change (the aging or growth of the population) and includes the effect of both change in the prevalence of cardiovascular risk factors and access to health care. The sum of these three components is equal to the observed change in the total number of deaths.

Global Deaths Due to Cardiovascular Disease

In 2013, the number of people who died from cardiovascular disease was more than 17.3 million (95% uncertainty interval, 16.5 to 18.1 million) in the 194 countries included in the study, representing an increase from 1990 of 40.8% (95% uncertainty interval, 34.4% to 46.4%), despite a decrease in cardiovascular deaths attributable to epidemiologic changes of 39.3% (95% uncertainty interval, 33.6% to 44.1%). The increase was driven by the change in the number of cardiovascular deaths attributable to demographic changes, with 30.2% (95% uncertainty interval, 28.1% to 32.3%) of the change in the number of global cardiovascular deaths attributable to change in age, sex, and cause of death. The change in age-specific death rates within World Bank income strata. GDP was obtained from a complete time series of country-specific GDP per capita, expressed in 2005 international dollars, for the years 1990 and 2013.
### Global Deaths and Cardiovascular Disease

#### Percentage/Change/Due/Each/Factor

<table>
<thead>
<tr>
<th>Region</th>
<th>Percentage Change Due to Population Growth</th>
<th>Change due to Population Aging</th>
<th>Change due to Age-specific Cardiovascular Death Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western sub-Saharan Africa</td>
<td>175</td>
<td>150</td>
<td>25</td>
</tr>
<tr>
<td>Oceania</td>
<td>125</td>
<td>113</td>
<td>12</td>
</tr>
<tr>
<td>South Asia</td>
<td>100</td>
<td>97.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>75</td>
<td>74.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Central Latin America</td>
<td>125</td>
<td>124</td>
<td>1</td>
</tr>
<tr>
<td>Central sub-Saharan Africa</td>
<td>100</td>
<td>97.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Andean Latin America</td>
<td>75</td>
<td>74.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Eastern sub-Saharan Africa</td>
<td>25</td>
<td>24.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Southern sub-Saharan Africa</td>
<td>50</td>
<td>49.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Tropical Latin America</td>
<td>25</td>
<td>24.7</td>
<td>0.3</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>75</td>
<td>74.6</td>
<td>0.4</td>
</tr>
<tr>
<td>East Asia</td>
<td>50</td>
<td>49.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Caribbean</td>
<td>25</td>
<td>24.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Central Asia</td>
<td>125</td>
<td>124</td>
<td>1</td>
</tr>
<tr>
<td>High-income Asia Pacific</td>
<td>100</td>
<td>97.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>50</td>
<td>49.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Central Europe</td>
<td>25</td>
<td>24.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Southern Latin America</td>
<td>75</td>
<td>74.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Australasia</td>
<td>50</td>
<td>49.6</td>
<td>0.4</td>
</tr>
<tr>
<td>High-income, North America</td>
<td>25</td>
<td>24.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Central Europe</td>
<td>125</td>
<td>124</td>
<td>1</td>
</tr>
<tr>
<td>Western Europe</td>
<td>100</td>
<td>97.5</td>
<td>2.5</td>
</tr>
</tbody>
</table>

#### Figure 2. Contribution of Changes in Population Growth, Population Aging, and Rates of Age-specific Cardiovascular Death to Changes in Cardiovascular Mortality, 1990–2013.
Atrial fibrillation or flutter and peripheral vascular disease are notable exceptions to the demographic and epidemiologic pattern for cardiovascular disease. Deaths from each of these conditions increased dramatically between 1990 and 2013, driven not only by population growth and aging but also by increases in age- and sex-specific death rates. However, the absolute numbers of deaths ascribed to these conditions remained relatively low as compared with those ascribed to ischemic heart disease and stroke.

**CARDIOVASCULAR DEATHS ACCORDING TO REGION**

The percentage change from 1990 to 2013 in the total number of deaths from all cardiovascular causes varied significantly by region (Fig. 2). In absolute terms, South Asia had the largest estimated increase in deaths from cardiovascular disease, reporting more than 1.7 million more deaths in 2013 than in 1990. This change represents an increase of 97.4% (95% uncertainty interval, 72 to 126.1). East Asia reported more than 1.2 million additional deaths in 2013, representing a 47.2% increase from 1990. The only regions with a significant decrease in cardiovascular deaths were Central Europe and Western Europe, which had declines of an estimated 5.2% and 12.8%, respectively. Southern Latin America, Australasia, and high-income North America had no detectable change in the number of deaths from 1990 to 2013 (as indicated by an uncertainty interval crossing 0) because population aging and growth balanced out declines in age-specific death rates. According to our estimates, epidemiologic change led to an increase in cardiovascular deaths in only one region of the world (western sub-Saharan Africa).

The combined effects of population growth, population aging, and changing age-specific death rates underlie the disparate trends in total cardiovascular deaths observed across world regions. To better understand these complex interactions, we categorized the regions into six general demographic and epidemiologic patterns (Table 2). Categories 1, 2, and 3 represent regions in which population aging and population growth served to drive relative increases in the number of cardiovascular deaths. Categories 4, 5, and 6 represent regions in which gains in cardiovascular health, represented by declines in the age-specific cardiovascular death rate, appear to have partially or completely negated the increase in cardiovascular deaths due to population growth and aging. For example, deaths in the high-income Asia–Pacific region have increased since 1990, but not as much as would have been seen if large declines in the risk of cardiovascular death had not occurred. Smaller relative gains in health, paired with a lesser degree of population aging, account for the decline in total cardiovascular deaths in Western Europe.

**CARDIOVASCULAR DEATHS AND NATIONAL INCOME PER CAPITA**

In order to investigate the relationship between national income per capita and the contribution of the age-specific death rate to cardiovascular mortality, we examined the correlation in these values between 1990 and 2013 in countries categorized by the World Bank as low income, lower-middle income, upper-middle income, and high income. Most countries had an increase in income per capita and a decline in the number of cardiovascular deaths due to epidemiologic change. However, the two variables had a significant correlation only within the category of upper-middle income. Pearson's correlation coefficients for the four levels of income were as follows: low income, r = 0.20, P = 0.24; lower-middle income, r = -0.08, P = 0.60; upper-middle income, r = 0.33, P = 0.02; and high income, r = -0.19, P = 0.18. Spearman's rho coefficients were as follows: low income, r = 0.16, P = 0.37; lower-middle income, r = -0.14, P = 0.35; upper-middle income, r = -0.37, P = 0.006; and high-income, r = -0.27, P = 0.05 (Fig. 3).

**DISCUSSION**

Our analysis of the global trends in cardiovascular mortality shows the degree to which population aging and growth have offset reductions in cardiovascular mortality over the past two decades. For the most common cause of cardiovascular death, ischemic heart disease, the number of deaths increased by an estimated 41.7% from 1990 to 2013. Population aging contributed to an estimated 52.5% increase in these deaths, whereas population growth contributed to an estimated 23.6% increase. On the basis of these estimates, large reductions in the age-specific risk of death from ischemic heart disease have led to almost 2 million fewer deaths than would have been expected had death rates remained unchanged from 1990.

Dramatic reductions in cardiovascular deaths due to epidemiologic change can be seen in some regions, especially in high-income countries. These
changes are probably due to the combined effect of birth cohorts’ decreased exposure to tobacco smoking, improvements in diet, and improved treatment of cardiovascular disease and cardiometabolic risk factors targeting the prevention of cardiovascular disease, and improved treatment of cardiovascular disease.10 For example, the most dramatic declines in the prevalence of tobacco smoking have occurred in high-income regions, including Japan, South Korea, Canada, Italy, Germany, and the United Kingdom.11 A deterministic health policy model indicated that 40 to 55% of the decline in coronary heart disease in high-income countries can be attributed to the effects of medical and surgical treatments.12 However, the determination of the causes of the decline in age-specific rates of cardiovascular death is beyond the scope of our analysis.

In the high-income Asia–Pacific region, the potential for an increase in cardiovascular mortality caused by a rapidly aging population appears to have been limited by the world’s largest decline in age-specific rates of cardiovascular death. In contrast, South Asia had a dramatic rise in cardiovascular deaths due to population growth and aging without a significant decline in cardiovascular deaths due to epidemiologic change. North Africa and the Middle East offset a similar trend in population growth and aging with a significant decline in cardiovascular deaths due to both population growth and aging that were moderated by a fall in age-specific rates of death.

### Table 2. Patterns of Demographic and Epidemiologic Change in Cardiovascular Mortality.

<table>
<thead>
<tr>
<th>Category</th>
<th>Change in Cardiovascular Deaths, 1990–2013</th>
<th>Effect of Population Growth</th>
<th>Effect of Population Aging</th>
<th>Effect of Age-Specific Cardiovascular Death Rate</th>
<th>Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category 1 — Population growth and aging: Regions with large and continuous increases in the number of cardiovascular deaths due to population growth or aging but little change in age-specific rates of death</td>
<td>Increase</td>
<td>Large (&lt;20%)</td>
<td>Large (&gt;30%)</td>
<td>Small (decline &lt;30%)</td>
<td>Oceania, South Asia, Southeast Asia, Caribbean</td>
</tr>
<tr>
<td>Category 2 — Population growth: Regions with increases in deaths due mostly to population growth</td>
<td>Increase</td>
<td>Large (&gt;80%)</td>
<td>Small (&lt;10%)</td>
<td>Small (decline &lt;30%)</td>
<td>Central sub-Saharan Africa, Western sub-Saharan Africa, Eastern sub-Saharan Africa</td>
</tr>
<tr>
<td>Category 3 — Population aging: Regions in which cardiovascular deaths rose and then fell during the preceding 20 years, resulting in a net increase in deaths due to population aging and only a small decrease in age-specific rates of cardiovascular death</td>
<td>Increase then decrease</td>
<td>Very small (&lt;20%)</td>
<td>Moderate (&gt;20%)</td>
<td>Very small (decline &lt;15%)</td>
<td>Eastern Europe, Central Asia</td>
</tr>
<tr>
<td>Category 4 — Improved health moderating effect of population aging: Regions in which large increases in the number of cardiovascular deaths due to population aging were moderated by a fall in age-specific rates of death</td>
<td>Increase</td>
<td>Small (&lt;30%)</td>
<td>Very large (&gt;70%)</td>
<td>Large (decline &gt;30%)</td>
<td>High-income Asia–Pacific, East Asia</td>
</tr>
<tr>
<td>Category 5 — Improved health moderating effect of population growth and aging: Regions with large relative increases in the number of cardiovascular deaths due to both population growth and aging that were moderated by a fall in age-specific rates of death</td>
<td>Increase</td>
<td>Large (&gt;30%)</td>
<td>Large (&gt;30%)</td>
<td>Large (decline &gt;30%)</td>
<td>Central Latin America, Tropical Latin America, Andean Latin America, Southern sub-Saharan Africa, North Africa and Middle East</td>
</tr>
<tr>
<td>Category 6 — Improved health exceeding effect of population growth and aging: Regions in which large declines in age-specific cardiovascular death rates have led to only small increases or even a decline in the number of cardiovascular deaths despite the large effects of an aging population</td>
<td>Small increase or decrease</td>
<td>Small (&lt;40%)</td>
<td>Large (&gt;30%)</td>
<td>Large (decline &gt;30%)</td>
<td>Southern Latin America, Australasia, high-income North America, Central Europe, Western Europe</td>
</tr>
</tbody>
</table>
tion growth and aging that increase the number of cases. Rather than using crude overall death rates across large age ranges, epidemiologists could use age-specific death rates to benchmark the performance of the health care system in a given country over time. Particular attention will need to be paid to the calculation of the age-specific metric when measuring progress toward the goal chosen by the United Nations for 2025 — a 25% reduction in the probability of premature death due to cardiovascular disease among persons between the ages of 30 and 70 years.

Our analysis adds to the perspective of Yusuf and colleagues on the effects of cardiovascular disease in developing countries.13,14 As they have noted, the classic model of “epidemiologic transition” does not fully reflect the heterogeneity of the burden of cardiovascular disease across countries. Our analysis shows that without the effect of population growth and aging, epidemiologic change would have led to a reduction in the numbers of cardiovascular deaths in most regions. However, in regions where this decrease was relatively small (i.e., regions in category 1), the combined effect of population growth and aging poses the greatest threat. We also show that increases in GDP per capita do not correlate well with declines in age-specific risk. Therefore, governments should not expect economic growth alone to address their countries’ burden of cardiovascular disease.

There are several limitations to our approach. First, cause-specific mortality data are lacking or of limited quality in some countries. Ensemble models incorporate data on regional patterns of mortality and other available information to derive estimates for countries with limited records on...
mortality. As a result, our estimates of the global burden of disease may not account for the actual variation in cardiovascular mortality among some countries. However, the rigorous out-of-sample predictive validity testing used in GBD 2013 is cause for some confidence. Second, although the use of codes from the International Classification of Diseases for death certification is a long-standing and widely accepted practice, cardiovascular diseases are complex and often attended by coexisting conditions. Our standard approach of attributing each death to a single underlying cause is intentionally defined according to GBD 2013 methods for the purpose of comparability and clarity. However, there will be some degree of misclassification bias. For example, undiagnosed diabetes may have preceded ischemic heart disease, or atrial fibrillation may have caused ischemic stroke. Furthermore, the remarkable increase in the age-specific rate of death from atrial fibrillation probably reflects increases in the screening, recognition, and attribution of death to atrial fibrillation in addition to changes in disease epidemiology. Similarly, the number of deaths resulting from rheumatic heart disease may not be completely captured by vital records in regions in which the condition is endemic. Third, we selected what we believe to be a straightforward procedure for decomposing death rates. However, calculations made with the traditional Shapley method and other methods used in econometrics may produce different results. Finally, we recognize that patterns of disease burden vary not just between but also within countries. Any summary provided at the level of a region or country may mask significant disparities within that area.

In conclusion, we found that population aging and growth accounted for the increase in the number of global deaths from cardiovascular disease between 1990 and 2013, despite an overall decrease in age-specific death rates in most regions. In only a few regions have gains in cardiovascular health offset these demographic forces to a degree sufficient to cause a decline in the number of cardiovascular deaths.

The views expressed in this article are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute, National Institutes of Health, or Department of Health and Human Services.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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REFERENCES

Lecture: Pre-hospital Emergency Care in sub-Saharan Africa

Lecturer: Nee-Kofi Mould-Millman


ORIGINAL RESEARCH ARTICLES


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Emergency care occurs on a continuum. Developing prehospital emergency care systems that are integrated with in-hospital emergency care systems can be a sustainable and effective way to help address the large morbidity and mortality of acute disease in Africa. Unfortunately, development of such prehospital systems across Africa has been slow to progress for many reasons, including feared cost implications, no agreed optimal system structure and function, and poor advocacy. In November 2013, the African Federation for Emergency Medicine (AFEM) convened a second expert and stakeholder meeting in Cape Town, South Africa, with the objective of reaching consensus on a few position statements to facilitate advocacy and to guide the development of emergency care in Africa. The objective of this paper is to report the outputs and position statements emerging from the AFEM Out-of-Hospital Emergency Care Workgroup consensus process. The term “Out-of-Hospital Emergency Care” was agreed by consensus and defined by the Workgroup as a suitable umbrella term for use in Africa that refers to the full spectrum of emergency care that occurs outside healthcare facilities. Critical components of this system were defined, including first responder care (tier-one) systems, and prehospital care and emergency medical services (tier-two) systems. The Workgroup provided a practical, adaptable and flexible set of guidelines and expert recommendations to facilitate advocacy and development of out-of-hospital emergency care systems in needy African settings.

Future directions of the AFEM Out-of-Hospital Emergency Care Workgroup include creating an online Toolkit. This will serve as a repository of template documents to guide implementation and development of clinical care, education, transportation, public access, policy and governance.


Le terme « Soins d’urgence hors des centres hospitaliers » a été accepté par consensus et défini par le Groupe de travail comme un terme générique pouvant être utilisé en Afrique en référence à la gamme complète des soins d’urgence fournis en dehors des établissements de soins de santé. Les composantes essentielles de ce système ont été définies, notamment les systèmes de prise en charge par le premier intervenant (premier niveau) et les systèmes pré-hospitaliers de soins et de services médicaux d’urgence (deuxième niveau). Le groupe de travail a produit un ensemble de directives et de recommandations préconisées par les experts afin de faciliter le plaidoyer et le développement de systèmes de soins d’urgence hors des centres hospitaliers dans les régions africaines sinistrées.


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Peer review under responsibility of African Federation for Emergency Medicine.

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Background

There is an undisputed need for emergency care systems in Africa to help relieve the large burden of disease from acute and emergent conditions.\(^1\) The Disease Control Priorities in Developing Countries Project estimates that as much as 45% of deaths and 35% of disability-adjusted life years can be addressed by developing emergency care systems in low- and middle-income countries (LMICs).\(^3\)

Comprehensive emergency care occurs on a continuum.\(^4\) Prehospital care refers to the acute and emergency care delivered outside the walls of a fixed healthcare facility.\(^5\) All the steps leading up to, and following, prehospital care are critical to minimize a victim’s likelihood of death or disability. This “chain of survival” includes recognition of the emergency, bystander-initiated care, access to prehospital emergency care services, prehospital care delivery, emergency transportation, emergency centre care and definitive care.\(^5\)

Mock et al. previously demonstrated that in LMICs without formal emergency care systems, nearly 80% of deaths due to severe injury occurred in the prehospital setting.\(^6\) This landmark analysis quantified the burden of disease potentially averted through developing prehospital trauma care systems in low-resource settings. In 2005, the World Health Organization (WHO) advocated strengthening of integrated formal trauma care systems in low-resource settings to alleviate the burden of disease from injuries.\(^7,8\) Developing prehospital trauma care systems was emphasized as an integral component of this system.\(^8\) The World Health Assembly, in Resolution 60.22, recommended improved organization and planning for provision of trauma and emergency care as an essential part of integrated healthcare delivery.\(^9\)

In 2011, the African Federation for Emergency Medicine (AFEM), through a consensus process involving over 140 experts, proposed that local African stakeholders actively advocate for the development of prehospital emergency care systems as a health system priority in their country.\(^9\)

Prehospital emergency care systems in Africa

To facilitate development of sustainable, effective, low-resource prehospital trauma care systems across Africa, WHO recommends developing two tiers of prehospital care.\(^5\) In tier-one, large volumes of trained community members serve as first responders, thereby providing a cost-effective front line for rapid medical response. In tier-two, trained professional responders deliver more specialized prehospital care in a more formal, coordinated and integrated manner.\(^5\)

Although the WHO two-tiered approach was envisioned as a trauma care system, the applicability and suitability of extending this model to non-traumatic prehospital emergency care systems are appealing.

Reports from several African nations indicate small-scale success with the initial development of both tiers of prehospital care systems. In Ghana, Madagascar, Uganda and South Africa, tier-one systems were piloted using taxi-drivers, police officers, local councilmen and community laypersons, as community-based first aid responders.\(^17\) These programs demonstrated strengths of local-appropriateness, practicality, sustainability, and cost-effectiveness. In 2011, the African First Aid Materials Guidelines were developed by the Belgian Red Cross-Flanders, through advocacy by the WHO and World Bank, as a means to further promote locally-appropriate first responder (i.e. tier-one) training in African regions without formal prehospital care systems.\(^21\) Experts have called for a wide-spread educational dissemination of such material, from school children to the elderly population, across Africa.\(^23\)

In Rwanda, Malawi, Ghana, and Kenya, SMS text messaging, motorcycle-ambulances and traditional ambulance services with trained prehospital personnel were developed to facilitate delivery of formal prehospital care.\(^3,13-15\) These tier-two systems addressed a diversity of acute conditions, including emergency obstetric care, medical emergencies, and acute trauma care. Although generally cost-effective at alleviating the acute burden of disease, tier-two systems continue to prove financially and technically challenging to develop in low-resource African environments.\(^5,10-14\)

Objective

In 2013, AFEM convened a second expert and stakeholder meeting in Cape Town, South Africa, with the objective of reaching consensus on a few position statements to facilitate advocacy and to guide the development of emergency care in Africa. The AFEM Out-of-Hospital Emergency Care (OHEC) Committee facilitated one of three workgroups. The objective of this paper is to describe the consensus process and the position statements that resulted from that meeting.

Process and methodology

In total, 135 persons representing experts in African acute and emergency care, public health, medical education, and research were in attendance at the one day 2013 AFEM Consensus Conference, representing 18 African and 14 non-African countries. Thirty-eight of the conference participants (28% of the total) participated in the OHEC Workgroup consensus process. Key items for discussion were prepared by three OHEC Workgroup moderators (NMM, SdV, RN) and framed around the driving objective of the larger consensus conference i.e. to reach consensus on advocacy and development of emergency care systems in Africa.

To facilitate the discussion, the scope of emergency care was defined in a previous AFEM Consensus Conference as the provision of initial resuscitation, stabilization, and treatment to acutely ill and injured patients and delivery of those patients to the best available definitive care, regardless of their ability to pay.\(^9\) Consensus recommendations were expected to conform to the following principles: appropriate for integra-
tion into existing African health systems, cost-effective, have a measurable impact, and be scalable.

A background presentation was delivered by the moderators to the members of the OHEC Workgroup to equilibrate knowledge on the current-state of prehospital care in Africa, to review various care models, and to underscore some of the essential elements for prehospital emergency care systems advocated by worldwide authorities.

The OHEC Workgroup agenda was then separated into 3 content areas for detailed consensus group discussion: (1) terminology, (2) system development, and (3) advocacy. Consensus was decided by a majority vote after discussion of each content area. At the end of the consensus process, OHEC Workgroup outputs were shared with the larger group present at the AFEM Consensus Conference for further feedback or objections.

**Outputs**

**Terminology**

The OHEC Workgroup agreed that the terms “out-of-hospital,” “prehospital,” and “emergency medical services (EMS)” were used erroneously and interchangeably, as evidenced during group discussion and through pre-review of the African emergency care literature. The OHEC Workgroup concluded that consensus on an OHEC model, terminology and semantics must be reached prior to consensus discussions regarding system development or advocacy.

“Out-of-Hospital Emergency Care (OHEC)” was agreed by consensus and defined by the Workgroup as a suitable umbrella term for use in Africa which refers to the full spectrum of emergency care that occurs outside healthcare facilities. This broadly includes care delivered by both laypersons and professional responders. OHEC begins with first responder care upon the recognition of a perceived or actual medical emergency. Easy access to emergency care services is crucial, where OHEC is delivered in a timely, safe, and effective manner by a trained personnel or provider. OHEC culminates in locally-appropriate emergency transportation to the closest, most suitable level of care. In certain situations, it may be locally appropriate for patients to be treated and released at the scene, especially if only minor conditions are identified by appropriately trained and authorized personnel.

“First Responder Care (FRC)” refers to OHEC in which the first emergency medical interventions are provided by a trained person within the community at the scene of the patient. It includes care provided by a spectrum of trained individuals (e.g. those knowledgeable in first aid, cardiopulmonary resuscitation, and scene management) who are integrated within a community.

“Prehospital Care (PHC)” was agreed upon to refer to out-of-hospital emergency care delivered by a professional provider with the ability to provide transport to a healthcare facility. This includes all the key elements of OHEC, namely bystander-initiated care, easy access to emergency care services, provision of medical care by trained prehospital practitioners, and emergency transportation to the closest, most suitable formal healthcare facility.

“Emergency Medical Services (EMS)” refer to formalized prehospital care, provided by emergency care professionals who respond to medical emergencies within a well-defined jurisdiction. EMS refers to an established entity, agency or system, which is appropriately integrated into the existing OHEC and facility-based healthcare system, thereby facilitating the coordinated, timely, and safe provision of emergency care and transportation to the most appropriate healthcare facility.

“Tier-one System” was agreed, by consensus, to refer to the foundation of the OHEC provided by first responders on a community level. Examples of tier-one OHEC systems include taxi-driver or police officer trauma programs in several African settings, and the Emergency First Aid Responder (EFAR) System, developed in South Africa.

“Tier-two System” refers to the next level of the OHEC system which provides more specialized prehospital care. Examples of tier-two OHEC systems include national ambulance and maternal obstetric motorbike units.

In an effort to conceptually unify all the above terminology and concepts, an *Out-of-Hospital Emergency Care Model* was agreed upon in which OHEC is the umbrella term referring to first responder care (FRC), prehospital care (PHC) and emergency medical services (EMS), all integrated into a two-tiered structure (Figure 1).

Emergency care occurs in a continuum in which discrete phases of care occur in different settings, requiring varied resources and personnel. Figure 2 illustrates how the OHEC model plays an early and critical role within the African continuum of emergency care.

![Figure 1](image_url)  
**Figure 1** Model of African Out-of-Hospital Emergency Care (OHEC) systems.
The urgent need for the development of African OHEC systems superimposed with the local challenges to their development, including poor resources, lack of technical expertise, underdevelopment of in-hospital emergency care, compelled the OHEC Workgroup to adopt a practical approach to framing the discussion and reaching consensus around the development of OHEC systems.2,4–6,9,11

**WHY should OHEC systems be developed?**

Several international public health organizations and authorities have emphasized the importance of ubiquitous access by a population to safe OHEC, an integral component of emergency care, as a fundamental healthcare right, thereby providing a means to address the acute burden of disease in low-resource settings across Africa.

**HOW should OHEC development be accomplished?**

A dedicated individual or unified entity is urged to serve as the champion and catalyst for OHEC development, as an initial necessary step. Stakeholder input and buy-in, at the community, healthcare and governance levels, is critical and must occur in advance of implementation. A two-tiered system model approach is recommended. If there are no existing OHEC systems, we advocate developing community-based (tier-one) systems first, then layering on basic then advanced (tier-two) PHC systems. Where immature OHEC systems exist, we encourage the strengthening of community-based (tier-one) OHEC to support growing, formal (tier-two) PHC and EMS systems. Systems should be customized to address the needs of the local population, considering existing infrastructure, leading causes of morbidity and mortality, and integration within the larger healthcare system. Additionally, we support development efforts that build upon existing resources, such as existing forms of transportation and community health resources. Of note, we caution development of ‘Western-style’ ambulance systems as the initial and sole approach to OHEC development in low-resource African settings.

**WHAT should be the goal of the OHEC system?**

A well-defined and deliberate strategic plan, to include realistic short-, medium- and long-term objectives, is strongly encouraged. At both tiers, we advocate for the following attributes: accessible, timely, safe, effective, scalable, sustainable, cost-effective, and have a measurable impact/outcome. (The specific definitions and measurement metrics of these attributes will be subsequently defined by the OHEC Workgroup and available in an AFEM OHEC Toolkit.) Key components of the system (tier-one or tier-two) should include easy public access and awareness, timely, safe, effective, and appropriate transportation and medical interventions, effective modalities for communication, care delivery by trained care providers (first responders or professional), and must be supported by enabling policies or a legal framework. (The specific definitions and measurement metrics of these components will be subsequently defined by the OHEC Workgroup and available in an AFEM OHEC Toolkit.)

**WHO should develop these systems?**

While we advocate that a local individual or group champions OHEC development, we recommend that individuals or teams with previous expertise in the design, implementation, management and monitoring of OHEC systems are preferred and best suited for technical guidance during system development. Ideally, a collaborative of experts in emergency care, preferably those with expertise in OHEC and an understanding of the local public health needs, should develop these systems. However, in the absence of local expertise, we advocate seeking technical advice or assistance transferring knowledge and developing local capacity from expert organizations like AFEM.

**WHERE should development begin?**

OHEC priority and focus areas should be guided by a formal need assessment and be laid out in the aforementioned Strategic Plan. If OHEC systems exist, we recommend scale-up activities of effective and sustainable existing OHEC systems. We suggest targeting development of OHEC in one or more of the following three high-yield areas: (1) in population-dense regions, (2) regions with the highest morbidity or mortality, and/or, (3) in response to African health priority conditions, such as maternal care, trauma, paediatric respiratory and diarrhoeal illnesses, and malaria.

**Advocacy for development of Out-of-Hospital Emergency Care systems**

Across Africa, other non-healthcare agendas, including education, nutrition, and public infrastructure, compete with
healthcare for priority in investment and development.\textsuperscript{1,2,4} We lay out a practical approach and a roadmap to advocacy for developing OHEC systems in the low-resource settings of Africa.

\textbf{WHEN should system development be encouraged?}

The time is now to address both the current and growing burden of acute disease in Africa.

\textbf{WHY is advocacy necessary for OHEC system development?}

OHEC systems will help address the large burden of disease from emergency conditions in Africa, if implemented strategically. Informed advocates and champions may be best positioned to offer this perspective to local, national and international stakeholders. Informed advocates and champions should be vocal so that systems are developed with strong vision.

\textbf{WHO should advocate for the development of OHEC?}

Advocacy for OHEC should be driven by individuals, advocacy groups, medical professional groups, public health agencies, and/or governmental agencies functioning at the community, municipal, regional, national, and/or international level. Champions may originate from the public or private sector, or may be a partnership of the two. We encourage multi-disciplinary approaches to advocacy.

\textbf{WHAT components and attributes of OHEC systems should be promoted?}

As a first step, we recommend the development of a local Strategic Plan, which will serve as a blueprint and roadmap for short-, medium-, and long-term OHEC system development. We recommend this Strategic Plan be reviewed periodically. We recommend the OHEC system be developed in two tiers: first responder care (tier-one) and prehospital care & emergency medical services (tier-two). In settings with no existing tier-two systems, we advocate development and strengthening tie-one systems first to serve as the foundation, then subsequently layering on tier-two systems. In settings where immature OHEC systems exist, we recommend strengthening tier-one systems to form the foundation and to support growing tier-two systems. We encourage development of OHEC systems that are accessible, timely, safe, effective, scalable, sustainable, cost-effective, locally-appropriate, and have measurable impacts and outcomes. Where possible, we encourage that OHEC systems help address neglected, vulnerable, communities around larger, critical public health initiatives to develop OHEC systems.

\textbf{WHERE should advocacy occur?}

AFEM strongly encourages that OHEC advocates and champions solicit buy-in at three stakeholder levels: policy-makers, healthcare officials and local community members. Advocacy can also be targeted to international health and/or funding agencies.

\textbf{HOW should advocacy occur?}

Leading international health authorities, including the World Health Organization, the World Health Assembly, the World Bank, and the African Federation for Emergency Medicine, have advocated developing OHEC systems as an integral part of emergency care systems. We urge OHEC champions to reference existing advocacy and policy documents from these international agencies to bolster their efforts. We strongly recommend that local or regional (acute) burden of acute disease data be gathered and presented to stakeholders to mount an evidence-based argument for the development of OHEC systems. Champions should demonstrate specifically how OHEC systems could help address some of the local, national or regional public health priorities, such as MDGs and trauma care.

Published reports from other low-resource international settings exist which detail the benefit conferred by developing OHEC systems. We recommend these be showcased as success stories worthy of local emulation. Such evidence will be made available in the AFEM OHEC Toolkit. Local champions and advocates are also encouraged to creatively leverage opportunities around larger, critical public health initiatives to develop OHEC systems.

\textbf{Conclusions}

The large burden of acute disease in Africa can be substantially addressed by effective, integrated emergency care systems, of which non-hospital emergency care plays a critical role. The AFEM 2013 OHEC Workgroup consensus process proved an effective and productive method to arrive at expert agreement towards non-hospital based emergency care development and advocacy across Africa. ‘Out-of-hospital emergency care’ was strategically selected as an umbrella term to include both first-responder care (tier-one) and prehospital care (tier-two). Given the varied economic, technical and human resources’ challenges associated with developing emergency care systems in low-resource African settings, it was agreed that ‘Western-style’ emergency medical services (EMS) systems represent the most costly and specialized of several approaches to building effective tier-two care systems appropriate for Africa.

It is our hope that these consensus statements will help promote the advancement of out-of-hospital emergency care across needy African settings. Subsequent efforts by the AFEM OHEC Workgroup will target the development of a Toolkit to serve as a repository of policy and technical documents to further assist the formation, growth and assessment of OHEC systems across Africa.

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Conflicts of interest

The authors declare no conflict of interest.

References

Emergency medical care in developing countries: is it worthwhile?

Junaid A. Razzak1 & Arthur L. Kellermann2

Abstract Prevention is a core value of any health system. Nonetheless, many health problems will continue to occur despite preventive services. A significant burden of diseases in developing countries is caused by time-sensitive illnesses and injuries, such as severe infections, hypoxia caused by respiratory infections, dehydration caused by diarrhoea, intentional and unintentional injuries, postpartum bleeding, and acute myocardial infarction. The provision of timely treatment during life-threatening emergencies is not a priority for many health systems in developing countries. This paper reviews evidence indicating the need to develop and/or strengthen emergency medical care systems in these countries. An argument is made for the role of emergency medical care in improving the health of populations and meeting expectations for access to emergency care. We consider emergency medical care in the community, during transportation, and at first-contact and regional referral facilities. Obstacles to developing effective emergency medical care include a lack of structural models, inappropriate training foci, concerns about cost, and sustainability in the face of a high demand for services. A basic but effective level of emergency medical care responds to perceived and actual community needs and improves the health of populations.

Keywords Emergency medical services/organization and administration; Delivery of health care; Health services accessibility; Primary health care; Triage; Transportation of patients; Cost of illness; Evidence-based medicine; Health care surveys; Developing countries (source: MeSH, NLM).

Mots clés Service médical urgence/organisation et administration; Délivrance soins; Accessibilité service santé; Programme soins courants; Orientation patients; Transport sanitaire; Coût maladie; Médecine factuelle; Enquête système de santé; Pays en développement (source: MeSH, INSERM).

Palabras clave Servicios médicos de urgencia/organización y administración; Prestación de atención de salud; Accesibilidad a los servicios de salud; Atención primaria de salud; Triaje; Transporte de pacientes; Costo de la enfermedad; Medicina basada en evidencia; Encuestas de atención de la salud; Países en desarrollo (fuente: DeCS, BIREME).

Introduction

Historically, global health policy emphasized multiple, vertically oriented programmes that concentrated on maternal and child health and the control of communicable childhood diseases (1). This resulted in major public health agencies focusing their support on selective programmes that address priority diseases and activities (2). Unfortunately, vertical programmes do not encourage the development of strong and efficient health care delivery systems. The weakness of this approach is most apparent during crises, such as medical emergencies or incidents involving large numbers of casualties.

Fortunately, experts in global health are beginning to take a more comprehensive view of health, including the provision of emergency medical care, than was traditionally the case. Thus the World Bank’s minimum package of health services includes six cost-effective interventions, one of which is a series of non-specialized interventions for emergencies, known collectively as limited care (3). WHO and UNICEF are placing substantial emphasis on the strengthening of triage and emergency care within the context of the integrated management of childhood illnesses (4).

Some governments are attempting to provide a basic package of emergency services. For example, shortly after independence in 1979, Mozambique made emergency care one of its four priority areas in health (5). One of the elements of the Health Investment Fund Project in the Republic of Moldova, funded by the World Bank, is the development of basic emergency care services (6). In Romania, the Health Sector Reform Project, supported by the World Bank, aims to improve emergency medical services as a key component of the overall health programme (7).

We make the case in the following paper for developing a simple but comprehensive approach to emergency medical care in developing countries.

Emergency medical care

The purpose of emergency medical care is to stabilize patients who have a life-threatening or limb-threatening injury or illness. In contrast to preventive medicine or primary care,
emergency medical care focuses on the provision of immediate or urgent medical interventions. It includes two major components: medical decision-making, and the actions necessary to prevent needless death or disability because of time-critical health problems, irrespective of the patient’s age, gender, location or condition.

Emergency medical care and health system performance

The three fundamental functions of a health system are to improve the health of the population, respond to people’s expectations, and provide financial protection against the costs of ill-health (8). Emergency medical care can contribute positively to these functions. There are no empirical data on the number of lives or disability-adjusted life-years (DALYs) saved through emergency medical care. Nevertheless, it is clear that many of the conditions that contribute to the burden of disease in low-income and middle-income countries can be mitigated through prompt treatment (Table 1).

Enhancing a health system’s responsiveness to people’s expectations leads to improved utilization of services and better outcomes (8). Access to medical care for urgent or life-threatening conditions is a key expectation in many communities. A study conducted in rural Nepal revealed that people used their primary health care centre more often for medical emergencies than for preventive services, such as family planning or prenatal care. The population perceived a strong need for accessible emergency medical and surgical services throughout the district (9). A survey conducted in two communities in Sri Lanka revealed that people expected to receive emergency care from the primary care system. In most instances they used traditional home remedies for minor ailments but turned to primary care medical facilities for acute complaints or when a child seemed seriously ill (10). In southern Nigeria, many women expressed a lack of faith in modern medical care for complications of pregnancy. However, they frequently sought hospital treatment for medical emergencies not amenable to cure by traditional methods. When asked to identify their health service priorities, they mentioned better training of health centre staff and the provision of ambulances for emergencies (11).

The role of emergency medical care in providing financial protection against the costs of ill health is complex. The onset of an acute illness or injury forces individuals and families to choose between risking financial ruin because of medical expenses or risking death or lifelong disability attributable to a lack of medical care. Both outcomes can have a catastrophic long-term impact. Prompt access to care during an emergency is essential, irrespective of whether the system gives financial protection through prepayment options, government provision of health care, or other insurance schemes.

Core components of emergency medical care

Emergency medical care has three components: care in the community; care during transportation, which is related to the question of access; and care on arrival at the receiving health facility. It is designed to overcome the factors most commonly implicated in preventable mortality, such as delays in seeking care, access to a health facility, and the provision of adequate care at the facility (12).

Emergency medical care in the community

The outcome of acute illness or injury is strongly influenced by early recognition of its severity and the need for medical intervention. Since most emergencies start at home, any system to promote the early recognition of emergency conditions should be based in the community. In order to save the lives of pregnant women it is important to reduce delays in accessing health care (13). In Zimbabwe a significant proportion of maternal deaths is caused by avoidable factors, including the failure of health workers to identify serious complications and to refer promptly women who are seriously ill to higher levels of care (14). Similarly, prompt referral of severely ill children to health services can reduce child mortality. In Mexico the training of mothers and first-level health care workers in the basic principles of triage led to care being sought more promptly and significantly reduced child mortality: deaths attributed to respiratory and diarrhoeal illness among children under 1 year of age decreased by 43% and 39%, respectively. Among children aged under 5 years, mortality caused by these conditions fell by 36% and 34%, respectively (15).

There are few data on the ability of lay persons and community health workers to learn to recognize life-threatening emergencies other than maternal and paediatric conditions. However, it is reasonable to assume that if a health worker can be trained to recognize severe blood loss in a postpartum woman, or breathing difficulty in an infant, he or she can also be trained to recognize severe blood loss in a trauma victim or breathing difficulty in an asthmatic adult. Many of the benefits of pre-hospital emergency care could be realized by teaching community volunteers simple but vital interventions, e.g. establishing and maintaining a patent airway, controlling external bleeding, and immobilizing fractures by means of local materials and resources (16).

Emergency medical care and transportation

An absence of emergency medical transport is a common barrier to care. This may arise because of any of several factors, including the lack of appropriate vehicles, the absence or inadequacy of roads, and the inability to pay for transport services. The consequences of a lack of transport can be grave. In urban Guinea-Bissau, 20 of 125 acutely ill children died either on their way to hospital or while waiting in the reception area of an outpatient clinic (17). In Malaysia a team assessing the value of the risk-coding system in pregnancy concluded that better communications, a more effective transport system, and better emergency care in hospitals were needed in order to reduce maternal mortality (18).

There is empirical evidence that providing emergency transport saves lives. In Sierra Leone, investment in a vehicle and an improved communication system led to a doubling of the utilization of emergency obstetric services and a 50% reduction in case fatalities (19). In Monterrey, Mexico, an increase in the number of sites of ambulance dispatch from two to four and the provision of basic skills training in trauma care reduced deaths among patients en route to hospital (20).

Disease-based interventions in emergency medical care can produce generalized benefits for populations. In Nigeria, for example, an emergency obstetric transport system transferred 29 women to higher levels of care over a period of two years. During the same period the system transported 27 men and children affected by other medical emergencies (21).
The prevailing models of emergency medical transport used in North America and Western Europe are quite costly and would be impractical for most low-income countries. Severe resource constraints, the poor condition of roads or trails, and a lack of fuel may dictate the utilization of a wider range of options. In the United Republic of Tanzania, for example, modes of emergency transportation include motorboats, canoes, bicycles with trailers, tricycles with platforms, tractors with trailers, reconditioned vehicles, and ox carts (22).

Emergency medical care at first-contact and referral facilities

The ready availability of treatment on arrival at a formal health care facility is the third component of emergency medical care. Health care facilities differ widely in respect of equipment, staff and resources, and they consequently possess varying capacities to provide emergency care. For this reason the level of care which can reasonably be expected at a primary care centre is significantly lower than that available at a tertiary care hospital. Nevertheless, some capacity to provide emergency care should be available at every level of a country’s health care system.

A health care facility’s capacity is determined by both human and structural factors. Human factors include the number and mix of health care workers and their level of training. Structural factors include space, medications, supplies and specialized equipment. The level of demand placed on the facility by the surrounding population may also dictate which services are offered and whether they can be accessed at short notice.

Health care facilities of poor quality produce poor outcomes (23–27). Initial triage and treatment constitute one of the weakest links in the system. A study in Malawi revealed that the condition of many seriously ill children arriving at clinics had not previously been recognized. Instead of receiving immediate emergency care they were kept waiting for long periods before being given proper treatment. This resulted in avoidable deaths and disability (28). In Mexico, verbal autopsies of 132 children who died revealed that the majority had been seen by a physician within three days of death. Poor selection of medications and late referral to tertiary care were judged to be important contributory factors in more than half the deaths (29). A qualitative study of 21 hospitals in seven developing countries found that poor triage of incoming patients and inadequate provision of emergency care jeopardized the lives of arriving patients (30). Fourteen of the facilities (including 10 of 13 district hospitals) did not have an adequate triage system. A comprehensive review of the management of 131 children treated at these facilities found evidence of inappropriate or delayed triage in 8% of cases, poor clinical assessments in 41%, and potentially harmful delays in treatment in 19%.

Several international health projects aimed at improving initial triage and treatment have been instituted at district health care facilities. Most focus on the strengthening of maternal and child health. One such project produced guidelines for emergency triage and treatment (28). An evaluation of these guidelines demonstrated that they significantly decreased the time required to assess children in need of urgent medical attention (31).

In Sierra Leone a health care facility was upgraded in order to enhance its ability to provide prompt medical and surgical treatment to women with complications of pregnancy. The annual number of obstetric procedures rose from 2 to 38 over a period of five years. During the same period the

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Table 1. Leading causes of deaths and disability-adjusted life-years (DALYs) in middle-income and low-income countries

<table>
<thead>
<tr>
<th>Causes of deaths</th>
<th>% of total deaths</th>
<th>Causes of DALYs</th>
<th>% of total DALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ischaemic heart disease</td>
<td>11.5</td>
<td>1. Lower respiratory infections</td>
<td>6.8</td>
</tr>
<tr>
<td>2. Cerebrovascular disease</td>
<td>8.9</td>
<td>2. Perinatal conditions</td>
<td>6.7</td>
</tr>
<tr>
<td>3. Lower respiratory infections</td>
<td>7.3</td>
<td>3. HIV/AIDS</td>
<td>6.6</td>
</tr>
<tr>
<td>4. HIV/AIDS</td>
<td>6.1</td>
<td>4. Meningitis</td>
<td>4.6</td>
</tr>
<tr>
<td>5. Perinatal conditions</td>
<td>5.1</td>
<td>5. Diarrhoeal diseases</td>
<td>4.6</td>
</tr>
<tr>
<td>6. Chronic obstructive pulmonary disease</td>
<td>4.7</td>
<td>6. Unipolar depressive disorders</td>
<td>4.0</td>
</tr>
<tr>
<td>7. Diarrhoeal diseases</td>
<td>4.4</td>
<td>7. Ischaemic heart disease</td>
<td>3.5</td>
</tr>
<tr>
<td>8. Tuberculosis</td>
<td>3.4</td>
<td>8. Malaria</td>
<td>3.0</td>
</tr>
<tr>
<td>9. Road traffic accidents</td>
<td>2.4</td>
<td>9. Cerebrovascular disease</td>
<td>2.9</td>
</tr>
<tr>
<td>10. Malaria</td>
<td>2.3</td>
<td>10. Road traffic accidents</td>
<td>2.8</td>
</tr>
<tr>
<td>11. Hypertensive heart disease</td>
<td>1.7</td>
<td>11. Tuberculosis</td>
<td>2.6</td>
</tr>
<tr>
<td>12. Measles</td>
<td>1.6</td>
<td>12. Congenital anomalies</td>
<td>2.3</td>
</tr>
<tr>
<td>13. Trachea, bronchus, lung cancers</td>
<td>1.6</td>
<td>13. Chronic obstructive pulmonary disease</td>
<td>2.3</td>
</tr>
<tr>
<td>15. Cirrhosis of the liver</td>
<td>1.4</td>
<td>15. Cirrhosis of the liver</td>
<td>2.0</td>
</tr>
</tbody>
</table>

* The causes of death for which evidence for saving lives with early intervention is available are shown with dark green background.
number of unscheduled non-obstetric procedures increased from 41 to 173 during the same period. Blood banks intended for use in obstetrical emergencies were used much more frequently for non-obstetric indications, such as surgical emergencies and trauma. The authors referred to these unanticipated benefits as ripple effects (32).

**Challenges to implementation of emergency medical care**

Beyond limited disease-specific or facility-specific interventions there are no successful models for systematically improving the overall provision of emergency medical care in developing countries. Fortunately, many countries already have programmes focused on emergency obstetric care and/or the integrated management of childhood illnesses. Such programmes may provide the necessary framework for creating a more inclusive, all-diseases approach to emergency programmes may provide the necessary framework for the integrated management of childhood illnesses. Such programmes may provide the necessary framework for creating a more inclusive, all-diseases approach to emergency medical care. It is important to note that, in many developing countries, the private for-profit and not-for-profit sectors are playing increasing roles in health systems (33). A broad programme such as emergency medical care requires wide consultation before it can be successfully implemented.

Despite the paucity of empirical data on emergency medical care in developing countries it is possible to specify the core components of such a system. They include: community education on accessing the emergency care system and administering first aid; simple communication systems for notifying the emergency care system of patients in need; transport, preferably motorized, for moving patients to the nearest health care facility; triage criteria to ensure efficient and timely utilization of existing resources at every level of the health care system; training of health centre personnel on the principles of emergency care; basic kits of instruments, supplies and medications enabling trained providers to give appropriate care at each level of the system.

The minimum standards for emergency medical care should be made clear, but it is not easy to define the emergency services to which everyone should have access. This matter should be discussed by communities, health care providers, health system researchers, policy-makers, ethicists and other interested parties. The framework for discussion should include, but not be limited to, the burden of disease, the availability of effective emergency interventions and the cost.

Rather than attempting to create an emergency medical care system de novo, planners should consider the use of established primary care centres. In addition to their traditional missions of providing preventive and primary care, these facilities could serve as casualty collection points for the initial evaluation and management of paediatric, maternal, trauma and medical patients with urgent problems. With proper training in the principles of triage and emergency stabilization, and a simple kit of essential equipment and supplies, the staff should be able to handle most problems on site. When a patient’s condition requires resources not possessed by a primary care centre, he or she could be transferred to the nearest hospital. The involvement of primary health care centres in the provision of emergency medical care should ensure that the greatest possible good is done for the largest possible number of people and should reduce the risk of district and regional hospitals becoming overwhelmed by non-emergency cases.

In addition to supplementing the knowledge and skills of professional providers at community health centres, low-income countries should consider implementing programmes for teaching the fundamentals of first aid to large numbers of volunteers. Initiating a few simple measures at the scene of an accident can do much good. The India Institute of Technology has produced a low-literacy manual for teaching basic first aid to both villagers and urban dwellers. It includes advice on using simple supplies and even local materials in order to accomplish vital tasks such as the control of bleeding and the immobilization of fractures (34). Once volunteers have been identified and trained the most motivated and talented can be recruited to transport victims to the nearest community health centres. A durable vehicle of sufficient size, with a few essential features and supplies, is sufficient for the vast majority of cases.

At the other end of the spectrum, attention should be given to the training received by physicians and other health care professionals. There is a marked disparity between what is taught in medical schools and what is expected of physicians in developing countries (35). Most medical students in developing countries acquire their training and skills on the inpatient wards of large tertiary care hospitals in urban areas, where emphasis is placed on making the right diagnosis rather than on the principles of triage and emergency management. This model may make sense in developed countries, where graduating physicians almost invariably obtain further training before engaging in independent clinical practice. However, it does not prepare physicians in developing countries for work in community health centres. In these facilities the most pressing requirement is to sort sick patients and make appropriate triage and treatment decisions. In order to do this well, doctors and nurses need to be trained to recognize the severity of illnesses and to categorize conditions in relation to the likelihood of a threat to life or limb, treatment priority, and the strategies most likely to maximize outcome, rather than on the basis of precise diagnoses. The training of health care providers in this manner requires a critical mass of physicians, nurses and other paramedical staff who understand the principles of emergency care and are prepared to exert pressure for their inclusion in the curricula of their respective disciplines.

The measures we describe are not particularly expensive and can benefit large numbers of patients. However, cost is still likely to represent a formidable barrier to implementing emergency medical care systems in developing countries. Depending on the extent of a country’s health care infrastructure, the implementation of an effective emergency medical care system may require little more than incremental reforms, or it may demand a major overhaul of the health care system.

Several small-scale experiments have examined the utility of cost recovery systems, private/community partnerships, and emergency loan funds for financing improvements to systems. All have met with some success (35). There are also successful models of private voluntary efforts for the provision of emergency medical transport. In Pakistan the Edhi Ambulance Service, a voluntary organization supported mainly through private and community donations, provides transport services to a large part of the country at minimal or no cost (36). Considerable savings could be achieved by recruiting citizens as volunteers helping to provide their own emergency care. The obstetric transportation system in Nigeria, outlined above, reported start-up costs of US$ 268 and had recurring costs of US$ 5.89 per transport.
Despite the encouraging experiments that have been conducted, doubts remain that investments in emergency medical care may divert resources from other preventive or curative programmes. This may be particularly problematic in countries with very limited resources. It may be difficult to gain public support for improvements in emergency medical care if they are built on funds taken from other worthwhile programmes.

The implementation of even a rudimentary emergency medical care system may have unintended consequences. The limited availability of even primary care services is a major concern, particularly in rural areas and highly impoverished communities. The few facilities that exist in these locations are already overburdened. If emergency medical care leads to an increase in the utilization of services the pressure on such facilities may become unbearable. Alternatively, if ambulance crews do not properly conduct triage by illness severity, people may use the emergency medical care system to bypass their community health centres and seek treatment at higher levels of care. The only way to determine if this is a legitimate concern is to conduct pilot programmes and assess their impact on both health care utilization and clinical outcomes.

Conclusion
Health care in developing countries has not traditionally focused on emergency medical care. Although health promotion and disease and injury prevention should be core values of any health system, many acute health problems will continue to occur. The incorporation of a basic level of emergency medical care into health care systems could have a significant impact on the well-being of populations. It would respond to the self-perceived needs of populations and decrease the long-term human and economic costs of illness and injury.

Priority should be placed on developing minimum guidelines for emergency medical care in low-income countries. The efficacy of such care could be assessed by implementing pilot programmes in several low-income and middle-income countries. This would help to determine the degree to which emergency medical care systems save lives and at what cost.

Conflicts of interest: none declared.
Access to out-of-hospital emergency care in Africa: Consensus conference recommendations

Christopher Stein, Nee-Kofi Mould-Millman, Shaheem De Vries, Lee Wallis

Access aux soins d'urgence hors de l'hôpital en Afrique : recommandations de la Conférence de concertation

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Access to out-of-hospital emergency care (OHEC) should be accessible to all who require it. However, available data suggests that there are a number of barriers to such access in Africa, mainly centred around challenges in public knowledge, perception and appropriate utilisation of OHEC. Having reached consensus in 2013 on a two-tier system of African OHEC, the African Federation for Emergency Medicine (AFEM) OHEC Group sought to gain further consensus on the narrower subject of access to OHEC in Africa. The objective of this paper is to report the outputs and statements arising from the AFEM OHEC access consensus meeting held in Cape Town, South Africa in April 2015. The discussion was structured around six dimensions of access to care (i.e. awareness, availability, accessibility, accommodation, affordability and acceptability) and tackled both Tier-1 (community first responder) and Tier-2 (formal prehospital services and Emergency Medical Services) OHEC systems. In Tier-1 systems, the role of community involvement and support was emphasised, along with the importance of a first responder system acceptable to the community in which it is embedded in order to optimise access. In Tier-2 systems, the consensus group highlighted the primacy of a single toll-free emergency number, matching of Emergency Medical Services resource demand and availability through appropriate planning and the cost-free nature of Tier-2 emergency care, amongst other factors that impact accessibility. Much work is still needed in prioritising the steps and clarifying the tools and metrics that would enable the ideal of optimal access to OHEC in Africa.

Les soins d’urgence hors de l’hôpital (OHEC) devraient être accessibles à tous ceux qui en ont besoin. Cependant, les données disponibles suggèrent qu’il existe un certain nombre d’obstacles à cet accès en Afrique, qui sont principalement liés aux difficultés en termes de connaissances du public des OHEC, de leur opinion sur ces derniers ainsi que de l’utilisation des OHEC appropriée par le public. Un consensus ayant été atteint en 2013 sur un système des OHEC d’Afrique à deux niveaux, le Groupe des OHEC de la Fédération africaine pour la médecine d’urgence (AFEM) a cherché à obtenir un consensus plus large sur le sujet plus précis de l’accès aux OHEC en Afrique. L’objectif de cet article est de rapporter les résultats et les déclarations issus de la réunion de concertation sur l’accès aux OHEC de l’AFEM tenue à Cape Town en Afrique du Sud en avril 2015. La discussion était organisée selon six dimensions d’accès aux soins (à savoir la sensibilisation, la disponibilité, l’accessibilité, le logement, l’abordabilité et l’acceptabilité) et a abordé les deux systèmes d’OHEC de Niveau 1 (premier intervenant au sein de la communauté) et de Niveau 2 (services prehospitaliers formels et services médicaux d’urgence). Dans les systèmes de Niveau 1, le rôle de la participation et du soutien communautaire a été souligné, ainsi que l’importance d’un système de premier intervenant acceptable pour la communauté dans laquelle il est intégré afin d’optimiser l’accès. Dans les systèmes de Niveau 2, le groupe de concertation a souligné la primauté d’un seul numéro d’urgence gratuit, le fait de faire correspondre la demande en ressources des Services médicaux d’urgence à la disponibilité grâce à une planification appropriée, et la gratuité des soins d’urgence de Niveau 2, entre autres facteurs ayant une incidence sur l’accessibilité. Un travail poussé est encore nécessaire en matière de classement des étapes par priorité et de clarification des outils et critères qui permettraient un accès idéal et optimal aux OHEC en Afrique.

Introduction

The adoption of World Health Assembly Resolution 60.22 established a landmark health care policy tool to improve emergency care access and availability globally with its call that “…a core set of trauma and emergency care services are accessible to all people who need them.” In November 2013, the African Federation for Emergency Medicine’s (AFEM) Out-of-Hospital Emergency Care (OHEC) Committee, through a consensus process, described a two-tier system for African OHEC: Tier-1 being first responder and community-based, whilst Tier-2 described formal prehospital services and emergency medical services (EMS).

Results of a recent Africa-wide EMS survey revealed that less than 9% of Africans are served by EMS, and the real number may be significantly less than 9% given multiple known barriers to accessing care. Two studies have specifically assessed barriers amongst African populations that impede their access to prehospital emergency care and...
transportation. Mould-Millman et al. concluded that perceptions of public ambulance services in Accra, Ghana, were generally favourable, although utilisation was low. The authors urged public health education as one intervention to help improve extremely low awareness of the toll-free medical emergency number and for education on the appropriate use of ambulances, whilst the transport and care capacity of local ambulance services were increased. These were felt to be priority pragmatic solutions to help minimise barriers to access and improve use of the EMS system. In Libreville, Gabon, investigators conducted a short oral interview of a small convenience sample of patients and visitors at a local emergency centre. Qualitative results from this study indicated that misperceptions, lack of awareness, alternative forms of transport, and cost were all barriers to accessing prehospital resources. Broccoli et al., through focus group discussions in Zambia, identified that barriers to access included the absence of emergency transportation, healthcare provider deficiencies, a lack of community knowledge, and a poor national referral system, amongst other issues.

The issue of appropriate access to OHEC is critical in matching demand and provision of valuable limited Tier-1 and Tier-2 resources: over-utilisation of these resources strains OHEC systems and thwarts their effectiveness, whilst under-utilisation results in wastage and cost-ineffectiveness.

In April 2015, AFEM held a third meeting in Cape Town, South Africa that included an OHEC consensus group. Following from the consensus statement in 2013, on advocacy and development of OHEC in Africa, the 2015 meeting focused on the narrower subject of access to OHEC in Africa. This paper’s objective was to describe the process and consensus statements on access to OHEC in Africa arising from this meeting.

### Process

After a set of plenary presentations on the morning of the 2015 AFEM Consensus Conference, three smaller groups broke away to focus on specific consensus discussions. One of these was the OHEC Access group comprising of ten participants with expertise in African OHEC systems. The OHEC Access consensus group discussion began with a short presentation (CS). This presentation provided background to the subject of OHEC access and reviewed relevant terminology, the Penchansky and Thomas’ conceptual frameworks of access to care, and barriers to access from the scientific literature.

Prior to the Consensus Conference meeting, two of the authors (CS and NMM) constructed a table with columns derived from the five dimensions of Penchansky and Thomas’ access model (Table 1). To this, a sixth dimension, awareness was added which was thought to be relevant to the discussion of access, and particularly in an African context. Awareness was defined as when and how members of a community access emergency care. Grid rows were a set of discussion foci based partly on the approach used in the 2013 AFEM Consensus Conference consisting of (i) principles of access (what should be in place to ensure adequate access), (ii) development of access (what needs to be done to ensure adequate access) and (iii) any other considerations relevant to access. This access grid was used to guide the consensus discussion that took place for the remainder of the day and its use was introduced and explained as the final part of the presentation.

As was the case with the 2013 AFEM Consensus Conference, discussions in the OHEC group aimed to produce recommendations that were applicable and could improve access to existing African OHEC systems that were cost-effective, implementable, measurable and capable of being scaled-up.

The agenda for the day was divided into access recommendations for Tier-1 (first-responder/community-based) and Tier-2 (EMS/prehospital care) OHEC systems. The access grid served as a framework for the consensus discussions and resultant majority-supported recommendations. All recommendations were briefly reviewed at the end of the day for final approval by all present at the general consensus conference.

### Outputs

Consensus outputs are divided into those relating to Tier-1 and Tier-2 systems, and are presented for each tier under subheadings of the six access factors identified above.

#### Tier-1 (First-responder/Community-based) Systems

**Awareness** – A single toll-free emergency telephone number should be known by all members in the community. The working group agreed this was likely the most important principle of access related to awareness in Tier-1. In addition, there should be broader knowledge in the community concerning how and when to activate Tier-1 and Tier-2 resources. The key driver for public awareness of EMS access was seen as community education. It was suggested that conventional methods of public education about access to OHEC could be utilised, but also that communities themselves could be a source for ideas on how best to achieve public education in an effective way.

**Availability** – Every effort should be made to encourage community engagement and involvement in order to increase the number of available community responders. The working group acknowledges that calculating an adequate number of commu-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Five dimensions of access to health care.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dimension</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Availability</td>
<td>The relationship of the volume and type of existing services (and resources) to the clients’ volume and needs</td>
</tr>
<tr>
<td>Accessibility</td>
<td>The relationship between the location of supply of services (or resources) and the location of clients</td>
</tr>
<tr>
<td>Accommodation</td>
<td>The manner in which the services (or resources) are organised to meet the needs of clients and clients’ perceptions of the appropriateness of the way services are organised</td>
</tr>
<tr>
<td>Affordability</td>
<td>The relationship between the cost and perceived value of services and the clients’ ability to pay</td>
</tr>
<tr>
<td>Acceptability</td>
<td>The relationship of the clients’ perceptions and attitudes towards the service (or resources) to the actual characteristics of the service, as well as to the perceptions and attitudes of providers towards certain clients</td>
</tr>
</tbody>
</table>
Tier-2 (EMS/Prehospital care) systems

Awareness – The existence of a single toll-free emergency number was seen as the most critical factor in facilitating awareness of how to access the EMS system. This needs to be closely coupled with education of the public on how to use this service appropriately. The problem of abuse and misuse of emergency numbers was mentioned as a barrier to access because inappropriate users tie up Tier-2 resources. Possible solutions to this problem include targeted public education, initial call screening to filter out abusive or hoax emergency calls and legislation making abuse of emergency numbers unlawful and subject to some form of sanction. The important role of community leaders in promoting appropriate use and discouraging abuse of emergency numbers was emphasised.

In addition to primary response, African Tier-2 systems are well positioned and critical in conducting inter-facility transfers of patients to higher levels of care for definitive management. Inter-facility transfers are largely executed by healthcare providers; hence the awareness and availability of Tier-2 resources must be made known to facility-based providers. Facility providers and Tier-2 systems must develop a system of timely transfers that is acceptable to patients, facility providers, and the Tier-2 system.

Availability – Matching the availability of Tier-2 resources with the timing and nature of community prehospital emergency care needs is critical. In order to optimise availability of EMS resources it was considered essential to know what the emergency care needs of a given community are. Such knowledge can be derived partly from the community, but perhaps more importantly, from ongoing accurate reporting of EMS incidents that can be historically analysed. Careful consideration should also be given to the type of EMS provider relative to the emergency care needs of a community, meaning that EMS training and scopes of practice should be closely aligned with these needs. Inappropriate EMS activation, which delays and consumes Tier-2 resources, was identified as a barrier to resource availability and steps were suggested to minimise this by including better EMS call-taking procedures, education on the role of EMS in a community, and close involvement of community leaders in information dissemination.

Accessibility – Location and positioning of resources plays a critical role in determining adequate accessibility. Conversely, the negative impact of poor location decisions can have an impact on restricting access to available resources. Two major factors were highlighted in this respect. The first is that barriers to access in a given EMS system must be understood if they are to be effectively overcome. And the second is that a substantial challenge in EMS access is the location of patients in (usually, densely populated) areas where formal systems of geographic addressing are not in use. In solving the patient location problem, it was emphasised that in many countries existing technology (i.e. cellular networks) can be used very effectively for this purpose if encouraged and enabled to do so. The optimisation and opening up of existing technology to improve patient location and EMS accessibility should be a focal point of advocacy by EMS providers, community leaders, professional associations and other OHEC interest groups.

Other innovative solutions may be effective in facilitating the location of patients by EMS, with or without the use of existing technology as recommended above. In many places where locating patients is a challenge, EMS vehicles are directed to well-known landmarks where they rendezvous with patients or with a guide who can take the vehicle to the patient’s location if the patient cannot be moved. Although workable, this approach may be improved by the establishment of predetermined and clearly marked rendezvous points well known to EMS providers and dispatch officers. It may also be possible to establish some kind of EMS communication at each rendezvous point. The involvement of community leaders and Tier-1 providers can enhance public knowledge of these rendezvous points and how to use them, thereby improving accessibility.

Accommodation – EMS should be available at all times, to all members of a community. Having EMS personnel available on a 24-h basis may be particularly challenging in less well developed or smaller systems, however, it is recommended that an attempt be made to offer some service even if it is on a standby basis. Community liaising is an important aspect of ensuring that expectations of service delivery are in keeping with what the system can actually deliver. The feedback of community members who have interacted with the EMS should be proactively sought in order to ensure that such ser-
vice provision is perceived as being appropriate, and if not, to identify areas for improvement and alignment.

Affordability – EMS should be available to all members of a community at no cost, for emergency medical purposes. The ability to pay should never be a factor in deciding on the access of any individual or community to quality EMS, for emergency medical needs. However, the provision of quality EMS is costly, and funding such systems is always challenging. This burden should never be placed on users of the system, but is rather a governmental responsibility that should be provided for as part of a budgeting process. Consideration should be given to private-public partnerships, where appropriate, as a potentially sustainable funding strategy. Given the competition for funding within government processes, the existence of an efficient EMS that is spoken of highly by the community it serves, and a system meeting performance metrics, makes an easy case for appropriate allocation. An EMS system that has a reputation for being wasteful, inefficient and out of alignment with the needs of a community is difficult to defend from a budgeting perspective. Consequently, it should always be remembered that affordability is closely associated with all of the other access factors and does not exist as a consideration on its own.

Acceptability – Sensitivity to the community, and what it considers acceptable in the provision of health care, is an important barrier to consider and proactively minimise. A number of psychosocial, cultural, political, religious, and linguistic factors, some of which have been touched on above, were considered to be important in positing EMS to be acceptable to the community it serves. Sensitisation and training is an important opportunity to ensure that EMS personnel understand and are sensitive to a community’s needs, and also that personnel understand and embody professionalism. Building and maintaining links between EMS and other parts of the health care system, including traditional health care providers in a community, is also important in reinforcing the acceptability of EMS.

Conclusion

Access to emergency care is a critical principle in building sustainable and resilient health systems the world over. This realisation is made all the more challenging within the austere environments that characterise many African countries.

Minimising barriers to accessing Tier-1 and Tier-2 systems by the public is critical to ensuring appropriate, timely, equitable use of these limited, but valuable, resources. In this consensus process, we applied Penchansky and Thomas’ framework of domains of health access to exploring likely challenges and proposing pragmatic solutions relevant to Tier-1 and 2 systems in Africa. Special mention was also made about the importance of timely access by facility-based healthcare workers to Tier-2 resources to assist with conducting acute or emergency inter-facility transfers.

The above consensus process has attempted to identify the key factors that must be considered when attempting to develop and strengthen out-of-hospital emergency care systems. Much work is still needed in prioritising the steps and clarifying the tools and metrics that would enable such a process.

Conflicts of interest

The authors report no conflicts of interest.

Authors’ contributions

CS and NMM prepared the Consensus Conference meeting material with review and comment from SD and LW, CS and SD facilitated and moderated discussion at the meeting, CS drafted the manuscript and all authors contributed significantly to critical review and revision of the manuscript.

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References

Lecture: Surgery in Low-Resource Settings

Lecturer: David Kuwayama

Surgeons Without Borders: A Brief History of Surgery at Médecins Sans Frontières

Kathryn Chu · Peter Rosseel · Miguel Trelles · Pierre Gielis

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Abstract Médecins Sans Frontières (MSF) is a humanitarian organization that performs emergency and elective surgical services in both conflict and non-conflict settings in over 70 countries. In 2006 MSF surgeons departed on approximately 125 missions, and over 64,000 surgical interventions were carried out in some 20 countries worldwide. Historically, the majority of MSF surgical projects began in response to conflicts or natural disasters. During an emergency response, MSF has resources to set up major operating facilities within 48 h in remote areas. One of MSF strengths is its supply chain. Large pre-packaged surgical kits, veritable “operating theatres to go,” can be readied in enormous crates and quickly loaded onto planes. In more stable contexts, MSF has also strengthened the delivery of surgical services within a country’s public health system. The MSF surgeon is the generalist in the broadest sense and performs vascular, obstetrical, orthopaedic, and other specialized surgical procedures. The organization aims to provide surgical services only temporarily. When there is a decrease in acute needs a program will be closed, or more importantly, turned over to the Ministry of Health or another non-governmental organization. The long-term solution to alleviating the global burden of surgical disease lies in building up a domestic surgical workforce capable of responding to the major causes of surgery-related morbidity and mortality. However, given that even countries with the resources of the United States suffer from an insufficiency of surgeons, the need for international emergency organizations to provide surgical assistance during acute emergencies will remain for the foreseeable future.

Introduction

Médecins Sans Frontières (MSF) is an international humanitarian medical organization whose mandate is to provide “medical aid to people affected by conflicts, epidemics, natural and man-made disasters, regardless of race, religion, politics or gender [1].” It began as a small French organization providing humanitarian aid to war refugees in Cambodia and Afghanistan. In the past 37 years, MSF has significantly expanded and now provides medical assistance in both conflict and non-conflict settings in over 70 countries. While the scope of its current coverage includes HIV/AIDS, malnutrition, cholera, and mental health, its history and core mandate remain intricately linked with treating surgical disease. In 2006, MSF surgeons performed over 64,000 procedures in 125 surgical projects located in 20 countries across the globe [2]. Médecins Sans Frontières is organized into five operational centers, and each provides a wide range of surgical care. In 2008, the Belgian operational center deployed 34 surgeons, 17 obstetricians, and 29 anesthesiologists to 19 surgical programs in 14 countries. This article is devoted to the history and main approaches of the surgical programs of MSF–Belgium (hereafter referred to as MSF).

Emergency response

Historically, the majority of MSF surgical projects began in response to conflicts or natural disasters (Table 1). The
organization began its surgical work in 1983 during the Chad/Libyan war. In order to treat victims of war at the border, MSF established surgical services in a tent hospital in north Chad. Expatriate surgeons reached this remote hospital after a 4-day journey overland from Darfur, Sudan. In 2004, MSF organized surgical care in three towns in Eastern Chad for refugees from the Darfur (North Sudan) genocide. Tent hospitals were erected out of locally purchased materials. Logisticians—creative and resourceful individuals responsible for the set-up and maintenance of the operating room, as well as electricity, clean water, waste disposal, and supply of surgical instruments and dressings—scrambled to find ways of keeping sand and dust out of the sterile operating room (Fig. 1). Typically, MSF teams will travel long distances to reach people in need. In 2005 during the civil war in the Ivory Coast, the surgical team camped in a forest, sleeping under mosquito nets tied to trees, as they travelled to a hospital in the rebel zone (Fig. 2). Sometimes, MSF has strategically positioned teams before armed conflict begins in order to pre-empt the need for an immediate humanitarian response. In 2002, during a civil war in Liberia, MSF was already present in Monrovia when increased fighting resulted in hundreds of war wounded. The administrative offices and living compound were turned into a hospital, and operating rooms were quickly constructed.

During an emergency response, MSF has resources to set up major operating facilities within 48 h in remote areas. Inflatable tents (Fig. 3) like the one used in Kashmir after the earthquake of 2004, can house up to three operating

### Table 1: Emergency surgical missions of Médecins Sans Frontières (MSF), 1983–present

<table>
<thead>
<tr>
<th>Start Year</th>
<th>Country</th>
<th>Location</th>
<th>Main reason for entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Chad</td>
<td>Northern Chad</td>
<td>War</td>
</tr>
<tr>
<td>1985</td>
<td>Ethiopia</td>
<td></td>
<td>War</td>
</tr>
<tr>
<td>1988</td>
<td>Armenia</td>
<td></td>
<td>Earthquake</td>
</tr>
<tr>
<td>1989</td>
<td>Guinea C</td>
<td>Nzérékoré</td>
<td>War</td>
</tr>
<tr>
<td>1990</td>
<td>Liberia</td>
<td>Monrovia</td>
<td>War</td>
</tr>
<tr>
<td>1991</td>
<td>Yugoslavia</td>
<td>Sebenesiska</td>
<td>War</td>
</tr>
<tr>
<td>1992</td>
<td>Sierra Leone</td>
<td>Freetown</td>
<td>War</td>
</tr>
<tr>
<td>1992</td>
<td>Mozambique</td>
<td></td>
<td>War</td>
</tr>
<tr>
<td>1992</td>
<td>Angola</td>
<td>Kuito</td>
<td>War</td>
</tr>
<tr>
<td>1993</td>
<td>Somalia</td>
<td>Kismaayo</td>
<td>War</td>
</tr>
<tr>
<td>1994</td>
<td>Burundi</td>
<td>Ngozi</td>
<td>War</td>
</tr>
<tr>
<td>1994</td>
<td>Burundi</td>
<td>Karuzi</td>
<td>War</td>
</tr>
<tr>
<td>1994</td>
<td>Rwanda</td>
<td>Kabutare</td>
<td>Genocide</td>
</tr>
<tr>
<td>1994</td>
<td>Chechnya</td>
<td>Grozny</td>
<td>War</td>
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<tr>
<td>1995</td>
<td>Haiti</td>
<td>St. Marc</td>
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<td>Luena</td>
<td>War</td>
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<td>1997</td>
<td>Rwanda</td>
<td>Gisenyi</td>
<td>War</td>
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<tr>
<td>1999</td>
<td>Indonesia</td>
<td>Timor</td>
<td>War</td>
</tr>
<tr>
<td>2000</td>
<td>Indonesia</td>
<td>Irian Jaya</td>
<td>War</td>
</tr>
<tr>
<td>2001</td>
<td>Indonesia</td>
<td>Molucca Ambon</td>
<td>War</td>
</tr>
<tr>
<td>2003</td>
<td>Ivory Coast</td>
<td>Man</td>
<td>War</td>
</tr>
<tr>
<td>2004</td>
<td>Indonesia</td>
<td>Aceh</td>
<td>Tsunami</td>
</tr>
<tr>
<td>2004</td>
<td>Indonesia</td>
<td>Lambo</td>
<td>Tsunami</td>
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<td>Tine</td>
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<td>War</td>
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<td>Sudan</td>
<td>Darfur, Serif Umra</td>
<td>War</td>
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<td>2004</td>
<td>Sudan</td>
<td>Darfur, Kebkabiya</td>
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<td>2004</td>
<td>Pakistan</td>
<td>Kashmir</td>
<td>Earthquake</td>
</tr>
<tr>
<td>2006</td>
<td>Haiti</td>
<td>Cité Soleil (Port au Prince)</td>
<td>War</td>
</tr>
<tr>
<td>2007</td>
<td>Democratic Republic of Congo</td>
<td>Masisi</td>
<td>War</td>
</tr>
<tr>
<td>2008</td>
<td>Haiti</td>
<td>Gonaïves</td>
<td>Hurricane</td>
</tr>
</tbody>
</table>

* For MSF-Brussels only. MSF has five operational sections.

Guinea C: Guinea-Conakry
rooms, postoperative wards, and even an intensive care unit. For longer term services, a hospital with an operating room was constructed from several large transport containers in Bagh, Pakistan (Fig. 4). Whenever possible, existing infrastructure, such as a government hospital, will be used, although at times, such buildings will have to be completely rehabilitated (Fig. 5). One of MSF’s strengths is its supply chain. Large pre-packaged surgical kits, veritable “operating theatres to go,” can be readied in enormous crates and quickly loaded onto planes. These contain all the equipment needed to perform major abdominal surgery, including operating tables, respirators, surgical instruments, gowns, electrocautery, and medications—in short, everything necessary to provide life-saving procedures.

**Working with the public health sector**

In addition to providing emergency response, MSF provides surgical care in post-conflict contexts where a
continued gap in basic health services may exist for decades. After the end of the Liberian civil war in 2003, MSF remained in the country to rehabilitate primary health services as well as surgical care. In the Democratic Republic of Congo, MSF currently provides comprehensive health services in the post-conflict area of Lubutu, including elective and emergency surgical care. Whenever possible, MSF works with the local ministry of health to strengthen the delivery of surgical services within the public health system. For example, in the 1980s in southern Chad, MSF was given the responsibility of improving the primary health care services of two districts. Hospitals were rehabilitated and local staff were trained in both medical and surgical care. Because of the severe lack of surgeons in developing countries, in certain instances, MSF supports task shifting, or the allocation of tasks from one group to a lower cadre. In Somalia and Angola, surgical nurses were trained in basic operative skills because expatriate surgeons were frequently evacuated and there were no physicians in the area to cover the surgical needs. In Haiti and Chad, formal training of nurses and general doctors to provide anesthesia and basic surgical services has been successful. Enlisting community health workers in Mozambique for referral of surgical disease and basic wound care and first aid is also being examined.

Engaging the international surgical workforce

 Médecins Sans Frontières recruits surgeons from all over the world who can work with limited supplies and infrastructure while treating acute surgical disease safely and expeditiously. Most of the time, the contexts in which MSF works require general surgeons who are broadly trained and able to perform a range of procedures, including cesarean sections, intestinal resections, and fracture reductions. Usually, there are no referral hospitals available and the surgeon must be able to perform urological, obstetrical, orthopedic, and even basic neurosurgical procedures (Table 2).

If a setting becomes too unstable and the lives of the MSF staff are threatened, then a project will close. In 2008, MSF evacuated all expatriate volunteers from Somalia after a local staff member was killed. In early 2009, MSF provided medical and surgical assistance in Darfur, although many NGOs had been ordered to leave by Sudanese president Omar al-Bashir. However, after three volunteers were kidnapped, expatriate staff evacuated and programs significantly downsized.

Conclusions

Médecins Sans Frontières has provided surgical care worldwide for over three decades, working in varied contexts to provide emergency care in acute settings and surgical services as part of comprehensive health services in post-conflict settings. In stable contexts, MSF aims to strengthen local staff by rehabilitating infrastructure and training local staff whenever possible. However, as an emergency humanitarian aid organization, the principal objective is to provide life-saving assistance. When there is a decrease in acute needs (i.e., at the end of a war), when local capacity has been sufficiently strengthened, or when marginalized populations are no longer excluded from healthcare, then MSF might decide to close a program, or hand over services to the ministry of health or to another non-governmental organization. The long-term solution to alleviating the global burden of surgical disease lies in building a domestic surgical workforce capable of responding to the major causes of surgery-related morbidity and mortality. However, given that even countries like the United States suffer from an insufficiency of surgeons, the need for international emergency organizations to provide surgical assistance during acute emergencies will remain for the foreseeable future.

Acknowledgments

The authors are grateful to Nathalie Civet and Nathan Ford for their valuable correspondence.

Table 2  Ten common procedures in emergent and non-emergent settings

<table>
<thead>
<tr>
<th>Emergenta</th>
<th>Non-emergent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exploratory laparotomy</td>
<td>Cesarean section</td>
</tr>
<tr>
<td>Wound debridement</td>
<td>Incision and drainage of abscess</td>
</tr>
<tr>
<td>Limb amputation</td>
<td>Wound debridement</td>
</tr>
<tr>
<td>Chest tube placement</td>
<td>Manual placenta extraction</td>
</tr>
<tr>
<td>Skin graft</td>
<td>Dilatation and curettage</td>
</tr>
<tr>
<td>Fasciotomy</td>
<td>Exploratory laparotomy</td>
</tr>
<tr>
<td>Closed reduction of fracture</td>
<td>Skin graft</td>
</tr>
<tr>
<td>Bowel resection</td>
<td>Closed reduction of fracture</td>
</tr>
<tr>
<td>Colostomy</td>
<td>Chest tube placement</td>
</tr>
<tr>
<td>Burr holes for subdural hematoma</td>
<td>Herniorraphy</td>
</tr>
</tbody>
</table>

a Emergent setting defined as war, conflict, or natural disaster

References

Lecture: Global Oral Health

Lecturer: Elizabeth Shick


Dental caries prevalence and risk factors among 12-year old schoolchildren from Baghdad, Iraq: a post-war survey

Nibras AM Ahmed, Anne N Åstrøm and Nils Skaug
Bergen, Norway
Poul Erik Petersen
Geneva, Switzerland

Aim: To examine the prevalence of dental caries in 12-year-old schoolchildren from Baghdad after the end of the United Nations’ economic sanctions and to investigate related dental caries risk factors including gender, socio-demographic factors, oral hygiene and sugar intake. Design: A cross-sectional dental caries examination and questionnaire survey was conducted in 10 schools from west Baghdad. Methods: Dental examinations based on WHO criteria and questionnaire surveys were performed on 392 children. Water samples were collected and fluoride concentration assessed. Results: The mean DMFT and DF were 1.7 and 1.3. The rate of caries experience (DMFT>0) was 62%. DMFT increased significantly with higher education of the mother, not being embarrassed to smile, missing school due to dental pain and between-meals mode of drinking. Increased sugar consumption was associated with being a boy, having mothers with low education, living in a low socio-economic area and brushing at least once-a-day. Positive oral hygiene practices were higher for girls. Western sweet snacks were preferred and sweet tea was frequently consumed. The fluoride content in drinking water was too low for caries prevention. Conclusion: It is important to maintain the low prevalence of caries among children by increasing awareness and promoting oral health care strategies.

Key words: Dental caries, sugar intake, oral hygiene, Iraq
countries, and in several developing countries the prevalence rates are increasing. Twelve-year-olds represent a standard age category used by the WHO to assess and compare dental caries levels in the permanent dentition of children worldwide.

Dental caries is a multi-factorial disease. Conclusive evidence show an association between frequent sugars intake and dental caries. Shifts in caries prevalence have been noticed during wars when there were sugar cutbacks. In modern societies, dental caries prevalence and sugar consumption have also been linked to ethnic background, socio-economic class and parents’ educational level.

Few studies have investigated dental health in the Iraqi population. Previous reports on the sweet preferences and dental caries in Iraqi children demonstrated that the level of sugar intake was high and that sugar consumption was positively associated with DMFT scores. Urban individuals showed a much higher preference and consumption of sugar than their rural counterparts. Within the urban population, individuals who had lived longer in the city and who were from families with lower educational backgrounds had the highest levels of sugar consumption. Finally, the observed decrease in the caries prevalence among children after years of economic sanctions was attributed to the low availability and consequently low consumption of sugar during those years.

Focusing on 12-year-old schoolchildren from Baghdad, Iraq, this study addresses the following purposes; to assess the level of dental caries, oral hygiene and sugar consumption habits shortly after the end of sanctions; to examine socio-economic correlates of children’s caries experience and sugar consumption and to provide baseline information for planning and evaluation of oral health promotion programmes for Iraqi schoolchildren.

Material and methods

Study area

Iraq is located in the Middle East, having a total area of 437,072 km² and a total population of 26,074,906. About 4-5 million people live in the capital Baghdad. Baghdad is homogeneously divided by the Tigris River into a Western and Eastern section, which in turn is subdivided into many districts of varying socio-economic standards of living. All schools are public in Iraq and schoolchildren enter secondary school at the age of 12. Secondary schools are established by gender into girls’ and boys’ schools.

Study population and sampling procedure

The study population consisted of 12-year-olds attending secondary schools for boys and girls in western Baghdad. Five districts of varying socio-economic status were selected purposely for the present cross-sectional study. The districts chosen were densely populated, located in or close to the centre of the city with a well defined socio-economic status. Since schools in the low socio-economic areas had more students per class, two districts from each of the high and middle socio-economic areas were selected whereas only one district was chosen from the low socio-economic area. To meet the study objectives, the sample size was estimated to be a minimum of 384 participants. The sample size was calculated based on an assumed caries prevalence of 50% and a standard error of 5%. From each district two schools (one for boys and one for girls) were selected randomly. In each of the 10 schools selected, the first classroom (usually alphabetically listed as class A) was chosen. Each class consisted of approximately 25-45 students. Children were asked for their birth year and only those who confirmed that they were born in 1991 were invited to participate in the study. In case of need for more participants, additional children from the next class were asked to participate. In total, 392 12-year-olds (49% boys) were recruited for the study and the response rate was 99.7%.

The fieldwork took place in mid-October 2003 to allow for a higher student attendance. A legal permit and written statement was obtained from the Ministry of Education to conduct clinical oral examinations and questionnaire surveys in the classroom during school hours.

Data collection

A questionnaire was structured containing 42 questions on socio-demographic factors, perceived oral and general health, oral hygiene and oral diet. The questionnaire was constructed first in English and then translated into Arabic. A pilot study was conducted on 12-year-olds in Baghdad to validate the Arabic phrases used in the translation to match the local dialect and ensure the precise comprehension of the children. The Arabic version of the questionnaire was later back-translated into English. The schoolchildren were initially informed about the purpose of the study, the data anonymity and the free will to participate. Children were divided into sub-groups of 20 individuals. Each group was guided throughout the questionnaire by the supervisor first reading each question aloud. The supervisor kept strictly to the text of the questionnaire without expanding the meaning of the questions to avoid a guided questionnaire. Misunderstandings due to difficult sentence structure were clarified by rephrasing the questions to a simpler form. Care was taken that children answered all questions and did not duplicate each others’ answers.
**Social and demographic characteristics**

Socio-demographic characteristics were assessed in terms of gender, parents’ highest level of education and socio-economic status, which was classified according to the socio-economic area of the school they attended.

**Perceived oral and general health**

The children rated their oral and general health situation in four Likert-scale questions. Children were also asked if they had felt embarrassed to smile, missed school or experienced eating problems from dental pain.

**Oral hygiene and dental visiting habits**

Frequency of tooth cleaning was assessed in terms of more than once-a-day, once-a-day, several times a week and seldom/never. Cleaning teeth after eating, using a toothbrush or finger, using toothpaste, and visiting a dentist either for a regular check-up or for dental pain treatment were also assessed.

**Sugar intake**

The frequency of sugar snacks consumption was assessed in terms of chocolate/ice-cream/toffee, local sweets (usually in a form of pastry with nuts and syrup), cakes/biscuits and dates/date syrup (very sweet fruit traditionally consumed by many Iraqis) intake. Sweet drink intake was assessed in terms of sugared tea / milk and soft drinks. An additive index on sugar consumption ranging from scores 4 to 16 was constructed from questions regarding sugar snacks (i.e. chocolate, local sweets, biscuits and dates) with value 4 representing the least frequent intake and value 16 representing the most frequent intake. A sugar drink score ranging from 2 to 8 was also constructed as a sum score of sugared tea/milk and soft drinks intake with value 2 representing the least frequent intake and value 8 representing the most frequent intake. The mode and preferred time of day for eating and drinking were also assessed.

**Oral examination**

Oral examinations were performed in the classrooms under daylight using dental mirrors and ball-tipped WHO dental explorers (CPI probes). All examination instruments were sterilised in an autoclave. Cotton rolls were used to control salivation during examination. Examinations for dental caries by the main investigator and a calibrated dentist from Baghdad were carried out using the WHO standard criteria and procedures. The registration system records dental caries at the cavity level and uniform caries registration between the two examiners was observed.

**Water samples and fluoride concentration**

The river Tigris is the main source of drinking water in Baghdad. All water pipe systems originate from the water purification centre which is located by the main river stream. Water samples were collected from the schools’ drinking water and one school was chosen for each district. Another sample from the main river water purification centre was taken. Water samples were collected in special 30ml propylene tubes with screw caps. The samples were kept in a cool place and the level of water in the six water samples was marked to ensure no evaporation would occur during transfer. The samples were analysed in the Clinical Research Laboratory, Faculty of Dentistry, University of Bergen. The fluoride concentration was measured with a 9609 BN Model Fluoride Specific Electrode connected to Orion Research Model Ion Analyzer.

**Statistical analysis**

The Statistical Package for Social Science (SPSS version 12) was used for the analysis of data. Cross tabulation, Chi Square analysis and one way ANOVA were used for bivariate analyses. Multivariate analyses with sugar frequency sum score and DMFT as dependent variables were conducted using GLM ANOVA. The significance level was set at 5%.

**Results**

**Sample profile**

Table 1 shows distribution of the participants by socio-demographic factors. Significantly more girls reported a high level of father’s education ($p<0.05$). The educational levels of the parents were significantly associated with the socio-economic area of the children’s school ($p<0.001$).

**Caries experience**

The caries index for the study group as a whole was 1.7, and the D-component (DT) contributed most to the DMFT index in both boys and girls. The mean FT score was significantly higher for children having mothers with higher education, fathers with higher education and for residents of higher socio-economic areas, as compared to their counterparts in the opposite groups. Mean FT scores were also higher in girls than in boys while DT and MT scores showed minor variation according to gender, area or socio-economic status. DMFT scores varied with the mother’s education being significantly higher in children with mothers of higher education compared to those having mothers of lower education (Table 2).
Ahmed et al.: Dental caries in Baghdad, Iraq

The prevalence of dental caries (DMFT>0) was 62.0%. Corresponding figures for DT>0, MT>0 and FT>0 were 54.8%, 3.6% and 15.0%, respectively. There were no differences in dental caries prevalence rates measured by DMFT>0 between the different socio-economic areas or between boys and girls. FT>0 was significantly lower for children from the low socio-economic area compared to children from high and middle socio-economic areas. Figure 1 depicts the frequency of decayed teeth (DT>0) by tooth-type in the upper and lower jaws. Ninety percent of all decayed teeth were molar teeth and 59% of all decayed teeth were lower molar teeth.

**Self-reported dental health**

Substantial proportions of children reported “good” oral health (89.8%), “good” general health (82.7%) and high satisfaction with their dental status (87.5%). More girls reported “good” general health compared to boys (90.7% vs 74.9%, \(p<0.001\)). Regarding dental problems, about one fifth of the children reported to have missed school hours because of dental pain. Nearly half of the children reported having experienced eating problems and almost one fifth reported feeling embarrassed to smile because of their teeth. The self-reported dental impacts were similar for boys and girls.

| Table 1 Percentage distribution of participants by socio-demographic factors |
|---------------------------------|----------------|----------------|----------------|
|                                 | Boys (n=193) | Girls (n=199) | Total (n=392) |
| Father’s education              |              |                |                |
| Low                             | 29.5         | 20.6           | 25.0           |
| Intermediate                   | 24.9         | 22.6           | 23.7           |
| High                            | 45.6         | 56.8 *         | 51.3           |
| Mother’s education              |              |                |                |
| Low                             | 38.9         | 31.2           | 34.9           |
| Intermediate                   | 28.5         | 30.2           | 29.3           |
| High                            | 32.6         | 37.7           | 35.7           |
| Socio-economic area             |              |                |                |
| Low                             | 34.7         | 31.2           | 33.0           |
| Middle                         | 33.2         | 39.7           | 36.5           |
| High                            | 32.1         | 29.1           | 30.6           |

\(** p < 0.001, * p < 0.05\)

<table>
<thead>
<tr>
<th>Table 2 Mean DMFT index and standard deviation (sd) for 12-year-olds by socio-demographic factors and gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s education</td>
</tr>
<tr>
<td>DT (sd)</td>
</tr>
<tr>
<td>Low 1.3 (1.7)</td>
</tr>
<tr>
<td>Intermediate 1.2 (1.6)</td>
</tr>
<tr>
<td>High 1.4 (1.8)</td>
</tr>
<tr>
<td>MT (sd)</td>
</tr>
<tr>
<td>Low 0.09 (0.4)</td>
</tr>
<tr>
<td>Intermediate 0 (0)</td>
</tr>
<tr>
<td>High 0.06 (0.3)</td>
</tr>
<tr>
<td>FT (sd)</td>
</tr>
<tr>
<td>Low 0.1 (0.6)</td>
</tr>
<tr>
<td>Intermediate 0.2 (0.5)</td>
</tr>
<tr>
<td>High 0.5 (1) **</td>
</tr>
<tr>
<td>DMFT (sd)</td>
</tr>
<tr>
<td>Low 1.5 (1.8)</td>
</tr>
<tr>
<td>Intermediate 1.4 (1.7)</td>
</tr>
<tr>
<td>High 2.0 (2.2) *</td>
</tr>
<tr>
<td>Father’s education</td>
</tr>
<tr>
<td>DT (sd)</td>
</tr>
<tr>
<td>Low 1.4 (1.8)</td>
</tr>
<tr>
<td>Intermediate 1.2 (1.6)</td>
</tr>
<tr>
<td>High 1.3 (1.7)</td>
</tr>
<tr>
<td>MT (sd)</td>
</tr>
<tr>
<td>Low 0.09 (0.4)</td>
</tr>
<tr>
<td>Intermediate 0.02 (0.2)</td>
</tr>
<tr>
<td>High 0.05 (0.3)</td>
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<tr>
<td>FT (sd)</td>
</tr>
<tr>
<td>Low 0.1 (0.5)</td>
</tr>
<tr>
<td>Intermediate 0.2 (0.6)</td>
</tr>
<tr>
<td>High 0.4 (0.9) **</td>
</tr>
<tr>
<td>DMFT (sd)</td>
</tr>
<tr>
<td>Low 1.7 (2)</td>
</tr>
<tr>
<td>Intermediate 1.4 (1.7)</td>
</tr>
<tr>
<td>High 1.7 (2)</td>
</tr>
<tr>
<td>Socio-economic area</td>
</tr>
<tr>
<td>DT (sd)</td>
</tr>
<tr>
<td>Low 1.2 (1.5)</td>
</tr>
<tr>
<td>Middle 1.5 (1.7)</td>
</tr>
<tr>
<td>High 1.2 (1.7)</td>
</tr>
<tr>
<td>MT (sd)</td>
</tr>
<tr>
<td>Low 0.08 (0.4)</td>
</tr>
<tr>
<td>Middle 0.05 (0.3)</td>
</tr>
<tr>
<td>High 0.04 (0.2) **</td>
</tr>
<tr>
<td>FT (sd)</td>
</tr>
<tr>
<td>Low 0.01 (0.3)</td>
</tr>
<tr>
<td>Middle 0.3 (0.7)</td>
</tr>
<tr>
<td>High 0.4 (0.9) **</td>
</tr>
<tr>
<td>DMFT (sd)</td>
</tr>
<tr>
<td>Low 1.3 (1.7)</td>
</tr>
<tr>
<td>Middle 1.8 (1.9)</td>
</tr>
<tr>
<td>High 1.7 (2)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Boys DT (sd)</td>
</tr>
<tr>
<td>1.4 (1.7)</td>
</tr>
<tr>
<td>Girls DT (sd)</td>
</tr>
<tr>
<td>1.2 (1.6)</td>
</tr>
<tr>
<td>Boys FT (sd)</td>
</tr>
<tr>
<td>0.04 (0.3)</td>
</tr>
<tr>
<td>Girls FT (sd)</td>
</tr>
<tr>
<td>0.07 (0.3)</td>
</tr>
<tr>
<td>Boys DMFT (sd)</td>
</tr>
<tr>
<td>1.6 (1.9)</td>
</tr>
<tr>
<td>Girls DMFT (sd)</td>
</tr>
<tr>
<td>1.7 (1.8)</td>
</tr>
</tbody>
</table>

\(** p < 0.001, * p < 0.05\)
Oral hygiene and dental visiting habits

Sixty-three percent of all children reported tooth brushing at least once-a-day, 32.4% reported cleaning their teeth after meals, 78.1% made use of a toothbrush whereas 16.6% reported using their fingers instead. A total of 84.7% of children claimed to have their own toothbrush and 81.6% reported using toothpaste with a toothbrush to clean their teeth. Significantly more girls than boys confirmed using a toothbrush (91.5% vs 64.2%, \( p<0.001 \)), tooth brushing at least once-a-day (73.9% vs 51.8%, \( p<0.001 \)), having their own toothbrushes (94% vs 75.1%, \( p<0.001 \)) and using toothpaste (93% vs 69.9%, \( p<0.001 \)) whereas significantly more boys admitted using their finger instead of tooth brushing (26.4% vs 7%, \( p<0.001 \)). Three out of four children confirmed that they had visited a dentist during their lifetime with 28.7% of the reported visits for regular dental check-ups and 71.2% for dental pain treatment.

Consumption of sugar snacks and drinks

The mean sugar snack score for all the study participants was 9.2 (sd =2.6) and the mean sugar drink score was 5.65 (sd =1.3). The average sugar snack and drink scores were significantly higher for boys than for girls (\( p<0.001 \)). The sweets consumed most frequently more than once-a-day were chocolate/ice-cream/toffee (29%) followed by sugared tea/milk (40.9% for boys and 23.1% for girls, \( p<0.001 \)).

Table 3 Percentage distribution of sugar snacks and drinks intake and mean sugar sum score by gender (n= 392) among those who confirmed “at least once-a-day” intake

<table>
<thead>
<tr>
<th>Sugar snacks</th>
<th>Boys (n=193)</th>
<th>Girls (n=199)</th>
<th>Total (n=392)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chocolate/ice-cream/toffee</td>
<td>31.1</td>
<td>27.1</td>
<td>29.1</td>
</tr>
<tr>
<td>Local sweets</td>
<td>15.5 **</td>
<td>3.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Cakes/pastry</td>
<td>14.5</td>
<td>11.1</td>
<td>12.8</td>
</tr>
<tr>
<td>Dates and date syrup</td>
<td>11.4</td>
<td>7.5</td>
<td>9.4</td>
</tr>
<tr>
<td>Sugar drinks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugared tea/milk</td>
<td>40.9 **</td>
<td>23.1</td>
<td>31.9</td>
</tr>
<tr>
<td>Soft drinks</td>
<td>24.9</td>
<td>17.6</td>
<td>21.2</td>
</tr>
<tr>
<td>Mean Sugar snack score (sd)</td>
<td>9.5 (2.7) **</td>
<td>8.9 (2.4)</td>
<td>9.2 (2.6)</td>
</tr>
<tr>
<td>Mean sugar drink score (sd)</td>
<td>6.0 (1.2) **</td>
<td>5.32 (1.4)</td>
<td>5.65 (1.3)</td>
</tr>
</tbody>
</table>

* \( p<0.05 \), ** \( p<0.001 \)
by cakes/biscuits, dates and local sweets (*Table 3*). The drink consumed most frequently more than once-a-day was sugared tea/milk (31.9%), while 21% reported taking soft drinks more than once-a-day.

A higher proportion of boys than girls reported intake of local sweets more than once-a-day (*p*<0.001). Consumption of tea/milk with sugar more than once-a-day was also significantly more frequent in boys than girls (*p*<0.001). Boys also took their drinks “all in one go” more frequently than girls (*p*<0.05). Finally, girls had a significantly higher preference for taking sweetened drinks “after meals” compared to boys (*p*<0.05) (*Table 4*).

### Table 4 Percentage distributions of preferred mode and time of sugar snacks and drink intake by gender

<table>
<thead>
<tr>
<th>Preferred mode of sweet consumption</th>
<th>Boys (n=193)</th>
<th>Girls (n=199)</th>
<th>Total (n=392)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar snacks all in one go</td>
<td>40.9</td>
<td>40.7</td>
<td>40.8</td>
</tr>
<tr>
<td>Sugar drinks all in one go</td>
<td>67.9*</td>
<td>55.3</td>
<td>61.5</td>
</tr>
<tr>
<td>Preferred time for eating sweets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At mealtimes</td>
<td>3.6</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Between mealtimes</td>
<td>19.7</td>
<td>20.6</td>
<td>20.2</td>
</tr>
<tr>
<td>After meals</td>
<td>44.0</td>
<td>45.7</td>
<td>44.9</td>
</tr>
<tr>
<td>At all times</td>
<td>32.6</td>
<td>32.2</td>
<td>32.4</td>
</tr>
<tr>
<td>Preferred time for taking sugared drinks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At mealtimes</td>
<td>23.8</td>
<td>23.1</td>
<td>23.5</td>
</tr>
<tr>
<td>Between mealtimes</td>
<td>7.8</td>
<td>9.5</td>
<td>8.7</td>
</tr>
<tr>
<td>After meals</td>
<td>41.5*</td>
<td>32.2</td>
<td>36.7</td>
</tr>
<tr>
<td>At all times</td>
<td>26.9</td>
<td>35.2</td>
<td>31.1</td>
</tr>
</tbody>
</table>

* *p < 0.05

### Table 5 Unadjusted and adjusted mean scores and 95% CI for DMFT by socio-demographic and behavioural characteristics GLM ANOVA for potential confounding factors

<table>
<thead>
<tr>
<th>DMFT</th>
<th>Unadjusted Mean</th>
<th>95% CI</th>
<th>Adjusted Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother’s education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.5</td>
<td>1.2-1.8</td>
<td>1.6</td>
<td>1.3-2.0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>1.4</td>
<td>1.1-1.7</td>
<td>1.7</td>
<td>1.3-2.1</td>
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<tr>
<td>High</td>
<td>2.0</td>
<td>1.6-2.3</td>
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<td>1.8-2.7</td>
</tr>
<tr>
<td>Feeling embarrassed to smile</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.4</td>
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<td>1.5</td>
<td>1.1-1.9</td>
</tr>
<tr>
<td>No</td>
<td>1.7</td>
<td>1.5-1.9</td>
<td>2.1*</td>
<td>1.7-2.3</td>
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<tr>
<td>Preferred time for taking sugared drinks</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At mealtimes</td>
<td>1.7*</td>
<td>1.3-2.2</td>
<td>1.8</td>
<td>1.3-2.2</td>
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<tr>
<td>Between-meals</td>
<td>1.6</td>
<td>1.3-2.0</td>
<td>2.1*</td>
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</tr>
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<td>After meals</td>
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<td>1.3-1.9</td>
<td>1.9</td>
<td>1.5-2.2</td>
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<td>At all times</td>
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<td>0.9-2.2</td>
<td>1.3</td>
<td>1.0-1.7</td>
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<tr>
<td>Preferred mode of taking sugared drinks</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>All in one go</td>
<td>1.8</td>
<td>1.5-2</td>
<td>2.0*</td>
<td>1.6-2.3</td>
</tr>
<tr>
<td>By portions</td>
<td>1.4</td>
<td>1.2-1.7</td>
<td>1.6</td>
<td>1.2-1.9</td>
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<tr>
<td>Missing school</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.3**</td>
<td>1.8-2.8</td>
<td>2.3**</td>
<td>1.9-2.7</td>
</tr>
<tr>
<td>No</td>
<td>1.5</td>
<td>1.3-1.7</td>
<td>1.5</td>
<td>1.2-1.7</td>
</tr>
</tbody>
</table>

* *p < 0.05, ** *p < 0.001
Predictors of caries experience

GLM ANOVA with DMFT as dependent variables revealed statistically adjusted effects of the following socio-demographic and behavioural variables: mother’s education (F= 3.2, p<0.05), feeling embarrassed when smiling (F= 4.4, p<0.05), missing school due to problems with teeth (F= 16.6, p<0.001), intake of soft drinks between mealtimes (F=2.9, p<0.05) and having soft drinks “all in one go” (F=4.0, p<0.05). Unadjusted and adjusted mean DMFT scores are depicted in Table 5. Caries experience increased with higher educational status of mother, not feeling embarrassed when smiling, having missed school due to dental problems and different modes of soft drink consumption. The highest caries experience was found for those who preferred between-meals mode of drinking.

Predictors of sugar snacks frequency score

GLM ANOVA was carried out with sugar snack sum score as dependent variable and socio-demographic and behavioural characteristics as independent variables. The analysis revealed statistically significant effects of gender (F= 10.1, p<0.001), mother’s education (F=3.3, p<0.05), socio-demographic area (F=14.1, p<0.001) and tooth brushing (F= 4.7, p<0.05) when controlling for father’s education and self-reported family economic situation (Table 6). High consumption of sugar snacks was associated with being a boy, having mothers with low education, living in a low socio-economic area, and confirming brushing at least once-a-day.

Fluoride concentration of the water samples

There were no significant differences in the fluoride concentration between the five districts and the main Tigris river water supply. The mean fluoride concentration was 0.14 ppm.

Discussion

This study was conducted on 12-year-old Iraqi schoolchildren, representing the first generation brought up during years of economic sanctions, sugar restrictions and food rationing systems. The survey was limited to the capital; meanwhile, the profile probably applies to most settings in the country.

The present study provides evidence of relatively low caries prevalence and severity. These results are concordant to the study of Jamel et al.15 on the caries prevalence among 12-year-old children in Baghdad after United Nations’ sanctions were imposed. After five years of low sugar availability, DMFT had significantly reduced in 12-year-old schoolchildren, irrespective of their socio-economic backgrounds15.

DT contributed most to the DMFT scores indicating that untreated caries is a problem for the children investigated. The average DMFT scores were higher in children having mothers of higher education compared to children having mothers of lower education. A similar pattern was observed for the FT component in the bivariate analyses indicating a higher prevalence of treated carious lesions in children having mothers of higher education. As shown in Table 2, FT varied

<table>
<thead>
<tr>
<th>Sugar score</th>
<th>Unadjusted Mean</th>
<th>95% CI</th>
<th>Adjusted Mean</th>
<th>95% CI</th>
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<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>9.4**</td>
<td>9.2-10</td>
<td>9.5**</td>
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</tr>
<tr>
<td>Girls</td>
<td>8.9</td>
<td>8.6-9.2</td>
<td>8.7</td>
<td>8.4-9.2</td>
</tr>
<tr>
<td>Mother’s education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>10.3**</td>
<td>9.8-10.8</td>
<td>9.6*</td>
<td>9.1-10.1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>9.0</td>
<td>10.5-11.4</td>
<td>9.3</td>
<td>8.8-9.8</td>
</tr>
<tr>
<td>High</td>
<td>8.4</td>
<td>11.2-12.0</td>
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<td>9.2-8.1</td>
</tr>
<tr>
<td>Tooth-brushing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least once-a-day</td>
<td>9.4</td>
<td>9.0-9.7</td>
<td>9.5*</td>
<td>9.1-9.8</td>
</tr>
<tr>
<td>Seldom</td>
<td>9.0</td>
<td>8.6-9.5</td>
<td>8.8</td>
<td>8.3-9.2</td>
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<tr>
<td>Socio-economic area</td>
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<td></td>
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<tr>
<td>Low</td>
<td>10.8**</td>
<td>10.3-11.2</td>
<td>10.5**</td>
<td>9.9-11.0</td>
</tr>
<tr>
<td>Middle</td>
<td>8.7</td>
<td>8.3-9.1</td>
<td>8.7</td>
<td>8.3-9.2</td>
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<td>High</td>
<td>8.4</td>
<td>8.8-8.8</td>
<td>8.3</td>
<td>7.8-8.8</td>
</tr>
</tbody>
</table>

*p < 0.05, ** p < 0.001
systematically with socio-economic area, father’s education, and sex, reflecting better oral health awareness and access to dental treatment among girls than boys and among higher than lower socio-economic status groups. The higher mean FT component observed among girls than among boys might reflect a sex difference regarding consciousness over oral appearance. It has been shown that children who had a high frequency of soft drinks were more likely to develop dental caries than those who consumed water or milk. The average DMFT score in the present study was highest among children who reported between-meal consumption of sugared drinks.

The chocolate/ice-cream/toffee category was the sugar item most frequently consumed (29.1%) compared to local sweets (9.2%) and dates/date syrup (9.4%) indicating a higher preference for Western sweets. The higher frequency of local sweet consumption among boys could be due to the fact that such sweets can often be sold in public streets making them more easily accessible for boys in the Iraqi community.

Substantial proportions of children preferred their intake ‘after meals’ regarding both sugar snacks (44.9%) and sugar drinks (36.7%) (Table 3). As shown in Table 6, sugar consumption varied systematically with sex, mother’s education and socio-economic status being highest among low educated subjects and among less affluent socio-economic status groups. This confirms previous evidence, suggesting that unhealthy food habits are most common among boys and children of less educated parents. Mothers from a more educated background might observe and regulate the dietary habits of their children while mothers from a lower educational background might encourage higher consumption of sugared food as a form of indulgence and luxury. Olojugba and Lennon reported that sugar is regarded as a luxury item when it is first introduced or imported into a developing country. Therefore, children from higher social classes are initially those who consume sugared products and experience its oral health consequences. As the use of sugar evolves in a society, it becomes commonly available to the whole population and eventually children from low social classes might also experience an increase in the caries prevalence. Sugar availability was low in Iraq during the 13 years of sanctions and therefore consumption was restricted to rich families who could afford expensive sugar products. This study was carried out shortly after the end of the sanctions when sugar products had become commonly available to the whole population causing a sudden elevation in sweet consumption among the deprived. The results presented in the present study, suggesting an opposite social gradient for caries experience and sugar intake of Baghdad schoolchildren might reflect such a situation.

The degree of satisfaction and attitudes towards oral and general health were high for both genders; however, regular oral hygiene practices were reported more frequently for girls. Most children reported visiting the dentist for symptomatic treatment of dental caries rather than for early diagnosis and prevention.

Even though previous studies in Iraq have documented the fluoride concentration in drinking water, it was important to re-assess the fluoride level since concentrations can vary with time as a result of climate, precipitation and temperatures over the year. The fluoride concentration was too low to have had any preventive effect on dental caries.

In summary, dental caries prevalence was low in 12-year-old schoolchildren in Baghdad although untreated carious lesions were prevalent. Dental caries was mostly related to higher maternal education and harmful sweet beverage drinking habits. On the other hand, sugar consumption was related to lower maternal education and low socio-economic status. Treated dental cavities were significantly higher in those with higher parents’ education and among residents from the higher socio-economic area. It is important that countries with a low intake of free sugars do not increase the intake. At this stage it is crucial to increase awareness among children and their parents of the oral health consequences of high sugar consumption after the ending of the economic sanctions. In addition, community based oral health promotion, fluoride prevention programmes and preventive oriented public dental health care services should be made available and accessible to all Iraqi children and especially those from the disadvantaged population.

**Acknowledgments**

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**References**


Ahmed et al. Dental caries in Baghdad, Iraq

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The HIV/AIDS pandemic has become a human and social disaster, particularly affecting the developing countries of Africa, Southeast Asia, and Latin America. By the end of 2004, about 40 million people were estimated to be infected by HIV globally. The health sectors in many affected countries are facing severe shortages of human and financial resources, and are struggling to cope with the growing impact of HIV/AIDS. In most developed countries, the availability of antiretroviral treatment has resulted in a dramatic reduction in HIV/AIDS-related mortality and morbidity. In contrast, in the developing countries, there is little access to treatment, and access to HIV-prevention services is poor. The '3 by 5' initiative was launched by the WHO and UNAIDS in 2003 with the aim of providing antiretrovirals to three million people in developing countries by the year 2005. HIV infection has a significant negative impact on oral health, with approximately 40-50% of HIV-positive persons developing oral fungal, bacterial, or viral infections early in the course of the disease. Oral health services and professionals can contribute effectively to the control of HIV/AIDS through health education and health promotion, patient care, effective infection control, and surveillance. The WHO Global Oral Health Program has strengthened its work for prevention of HIV/AIDS-related oral disease. The WHO co-sponsored conference, Oral Health and Disease in AIDS, held in Phuket, Thailand (2004), issued a declaration calling for action by national and international health authorities. The aim is to strengthen oral health promotion and the care of HIV-infected persons, and to encourage research on the impact of oral health on HIV/AIDS, public health initiatives, and surveillance.

The HIV/AIDS Pandemic

The HIV/AIDS pandemic has become a human, social, and economic disaster, with far-reaching implications for individuals, communities, and countries. No other disease has so dramatically highlighted the current disparities and inequities in health-care access, economic opportunity, and the protection of basic human rights. By the end of 2004, about 40 million people were estimated to be infected with HIV (UNAIDS/WHO, 2004). During 2004, the HIV/AIDS pandemic claimed more than three million lives, and five million people became infected with HIV. Each day, there are 14,000 new HIV infections, more than half of these occurring among young people under 25 years of age. Over three million children are infected with HIV (UNAIDS/WHO, 2004). Global data available on the HIV/AIDS pandemic are illustrated in Figs. 1 and 2. Sub-Saharan Africa has been most severely affected, with almost 10% of the adult population being infected in 2004, and an estimated 25 million people living with HIV (UNAIDS/WHO, 2004). Life expectancy has fallen to below 50 years. Nearly 10% child mortality is HIV-associated, with a negative impact on the progress in child survival made during the past decades. In Southeast Asia, there are more than seven million people infected, and further spread could lead to millions more becoming infected in the coming decade. The epidemic in Latin America is well-established, with nearly two million people being infected, while rapid growth has been observed in recent years in Eastern Europe and Central Asia. Globally, the major mode of HIV transmission is through sexual intercourse, intravenous drug use, mother-to-child transmission, and contaminated blood in the health-care setting. The relative importance of the different modes of transmission varies between and within regions of the world.

HIV/AIDS and Society

In all affected countries with either high or low HIV prevalence, AIDS hinders development, exacting a devastating toll on individuals and families (US Agency for International Development, 2004). In the hardest-hit countries, it is eroding decades of health, economic, and social progress—reducing life expectancy by years, deepening poverty, and contributing to and exacerbating food shortages. Sub-Saharan Africa has the world’s highest prevalence of HIV infection and faces the greatest demographic impact. In seven African countries where HIV prevalence is more than 20%, the average life expectancy of a person born between 1995 and 2000 is now 49 years, which is 13 years lower than in the absence of AIDS. In Swaziland, Zambia, and Zimbabwe, which lack access to antiretroviral programs, average life expectancy is predicted to drop below the age of 35.

In some of the worst-affected countries, the living standards of many poor people deteriorated before they experienced the full impact of the HIV epidemic. In general, HIV/AIDS-affected households are more likely to suffer severe poverty than non-affected households; this is true for countries with low as well high prevalence rates. HIV/AIDS reduces the income and production of family members who are ill, at the same time creating extraordinary care needs, rising household medical expenses, and other costs which, on average, absorb one-third of a household’s monthly income.

The HIV/AIDS epidemic is also a significant obstacle to the universal access of children to primary education. In many countries of Africa, the epidemic is expected to contribute substantially to the future shortage of primary school teachers. As skilled teachers fall ill and die, the quality of education suffers. Children, especially girls, from AIDS-affected families are often withdrawn from schools to look after the home and

Key Words
Oral disease, HIV/AIDS, oral health care, prevention, WHO.

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to compensate for the loss of income through a parent’s illness and the expenses incurred to care for ill relatives.

**Health-care Systems**

The HIV epidemic has created a need for robust, flexible health-care systems. The health sector in many affected countries is facing severe shortages of human and financial resources, especially in the worst-affected countries of Africa and Asia. Many health services and facilities are struggling to cope with the growing impact of HIV/AIDS. In sub-Saharan Africa, people with HIV-related illnesses occupy more than 50% of hospital beds (UNAIDS/WHO, 2004). At the same time, demand for health services is increasing, as more health-care personnel are dying themselves or are unable to work as a result of AIDS. Therefore, more health-care personnel will need to be trained and new categories of health-care workers established (e.g., primary health workers, assistants, and health counselors). Lack of resources, too many competing demands, and lack of influence within government decision-making are demoralizing some health ministries, thereby hindering the overall national response to the pandemic.

In many developed countries, the availability of antiretroviral treatment has meant dramatic reductions in HIV/AIDS-related mortality and morbidity (WHO, 2004a). As a result, more people with HIV are able to enjoy better health and lead productive lives. This is in marked contrast to the developing countries, where there is little treatment access. Although prevention is the mainstay of the response to AIDS, fewer than one in five people worldwide have access to HIV prevention services. For young people, knowledge and information about prevention are the first line of defense. Meanwhile, AIDS education is still far from universal: Youth need access to sound health information as well as to condoms. The Table highlights the key elements in comprehensive HIV prevention.

**Treatment, Care, and Support for People Living with HIV**

Access to antiretroviral treatment and other HIV-related disease care remains low in developing countries. The WHO estimates that nine out of ten people who need urgent HIV treatment are not being reached (WHO, 2003a, 2004a). Approximately five to six million people in developing countries will die in the next two years if they do not receive antiretroviral treatment. Yet the global movement to scale up access to HIV treatment has made critical gains during the past few years. Never before have there been such high levels of financial resources to fund treatment, care, and support, or the strength of political will in countries to provide them. The price of many medicines and diagnostics has fallen dramatically. The ‘3 by 5’ initiative was launched by the WHO and UNAIDS in September, 2003, with the aim of providing antiretrovirals to three million people in developing countries by the end of 2005. The aim was an interim target only, the initiative being part of a global movement to mobilize support for, ultimately, universal access.

**National Responses to AIDS—The Political Context**

Political commitment has recently increased in the hardest-hit countries. In sub-Saharan Africa, as well as in some countries of Asia and the Caribbean, more leaders have taken personal responsibility for implementing a national AIDS response. However, in most countries where HIV is spreading quickly—for example, in Asia and Eastern Europe—the lack of leadership may result in a delayed response. Furthermore, in low-prevalence countries, where the epidemic is concentrated in key populations at high risk, especially sex workers and intravenous drug users, many political leaders remain detached from the response to AIDS.

Conscious of the need to define and strengthen the role of the health sector within a broad multisectoral response to HIV/AIDS, the World Health Assembly adopted a resolution in May, 2000 (WHA 53.14), requesting that the WHO develop a strategy for addressing HIV/AIDS as part of the United Nations Special Session on HIV/AIDS in 2001. The aim of the so-called ‘Global Health—Sector Strategy’ (WHO, 2003b,c) is to strengthen the response of the health sector to the challenges posed by HIV/AIDS as part of an overall multisectoral effort. The strategy describes the support that the WHO will offer,
and outlines a series of steps, issues, and action points for health ministries and others in the health sector to consider, especially during the development or updating of national strategic plans for HIV/AIDS. The major action points are: prevention and health promotion, diagnostic services and treatment, health standards and health systems, and informed policy and strategy development.

**Oral Health in HIV/AIDS**

Several studies have demonstrated the negative impact of HIV infection on oral health (Johnson et al., 2006). Approximately 40-50% of HIV-positive persons have oral fungal, bacterial, or viral infections that occur early in the course of the disease. Oral lesions strongly associated with HIV infection include pseudo-membranous oral candidiasis, hairy leukoplakia, HIV gingivitis and periodontitis, Kaposi’s sarcoma, and non-Hodgkin’s lymphoma (Coogan and Sweet, 2002). Dry mouth has been frequently observed in the course of HIV infection (Glick et al., 1994). Decreased salivary flow rate may not only increase the risk of dental caries but may also have a further negative impact on quality of life, because of difficulty in chewing, swallowing, and tasting food. There is a need for immediate oral health care and referral, the treatment and prevention of oral disease, and health promotion, particularly among the under-served, disadvantaged population groups of developing countries. In those countries, availability of and access to oral health care are generally low, because of shortages of oral health practitioners.

The World Health Organization (WHO) has worked to control HIV/AIDS-related oral conditions through several activities. The WHO Oral Health Program has prepared a guide (Melnick et al., 1993) which is intended to provide a systematic approach to the implementation of epidemiological studies of oral conditions associated with HIV infection; to provide guidelines for the collection, analysis, reporting, and dissemination of data from such studies; and to facilitate comparison of findings from different studies. It also aims to encourage oral health personnel and public health practitioners to make oral health status an integral part of optimum care management and the introduction of the surveillance of oral diseases associated with HIV infection.

**Capacity-building for the Oral Health Response to HIV/AIDS**

Oral health services and professionals can contribute effectively to the early diagnosis, prevention, and treatment of HIV/AIDS. Members of the oral-health-care professions, especially their medical and nursing colleagues, are powerfully placed to help ensuring that they and others understand the facts about AIDS and their responsibilities. They also are in a position to care for patients and to design and direct appropriate prevention and health promotion programs.

Recently, the WHO published a global overview of oral health, and the report also outlined the approach of the WHO Global Oral Health Program to promoting oral health during the 21st century (Petersen, 2003). The WHO sees oral health as an integral part of general health, and an essential component of quality of life. Oral manifestations of HIV/AIDS are considered a most important challenge to improved health in the future, particularly in developing countries.

In 1995, the WHO outlined some basic principles for developing a country-specific approach to capacity-building to control HIV/AIDS-related oral disease (WHO, 1995). Four areas were identified: (1) health promotion and health education, (2) patient care, (3) infection control, and (4) epidemiology and surveillance. Health promotion and health education are particularly needed to limit the spread of HIV and AIDS. Health promotion, education, and infection control must therefore be incorporated into the delivery of oral health services to patients. An overriding principle in patient care is the need for oral health providers to remain up-to-date on both the diagnosis and treatment of oral conditions associated with HIV infection, through consulting the scientific literature and attending continuing education courses. Infection control practices are based on the application of four principles of infection control: (a) take action to stay healthy, (b) avoid contact with blood, (c) limit the spread of blood, and (d) make objects safe for you. All members of the oral health team should be familiar with these guidelines for local infection control. Finally, surveillance of oral disease related to HIV infection, as well as risk factors, is essential to the planning and evaluation of public health programs. The WHO Oral Health Program has designed appropriate surveillance forms and systems based on sound epidemiological tools. Robust diagnostic criteria have been developed for the more common oral lesions found in HIV-infected individuals, and these criteria may provide for the establishment of an oral health component of global information systems in HIV/AIDS.

Recently, several countries have established guidelines for the control of the oral manifestations of HIV disease (WHO, 1995). Oral health professionals have been exposed to continuing education programs to improve their knowledge and skills to serve HIV-infected patients, and to prevent cross-infection in health-care settings. Such national programs are mostly available in industrialized countries, and still remain challenges in several developing countries. However, special efforts were made to strengthen control of HIV/AIDS-related oral disease in India, through the preparation of a handbook on HIV disease for dental professionals (Viswanathan and Ranganathan, 1999).

In developing countries, oral health services are mostly offered from regional or central hospitals of urban centers. The importance of preventive or restorative dental care is not stressed. Many countries in Africa, Asia, and Latin America have a shortage of oral health personnel, and the capacity of the systems is generally limited to pain relief or emergency care. In countries of Central and Eastern Europe, privatization of oral health services has taken place during recent years: Third-party payment systems have been introduced, but priority is not given to preventive oral care. Globally, the WHO Oral Health Program supports the development of oral health services that match the needs of the country, including the need to provide appropriate oral-health care for HIV-infected people.

**Strengthening the Prevention of HIV/AIDS-related Oral Disease**


The WHO Global Oral Health Program, in collaboration with other WHO technical programs and WHO Collaborating Centres in Oral Health, will facilitate and coordinate the expansion of successful initiatives through technical and managerial support. Such activities may focus on:

- identification of the most indicative oral manifestations of HIV/AIDS
- involvement of oral health personnel in the documentation of HIV/AIDS to ensure appropriate medical evaluation, prevention, and treatment
- training of other health professionals and primary health-care workers on how to screen for oral lesions and extra-oral manifestations; the ‘Train the trainer’ approach is used to reach health-care workers at local village community level. The WHO Oral Health Program has designed an oral health component of the project, Integrated Management of Adolescent and Adult Illness (WHO, 2004b). This project
intends to develop the capacity in primary health care of first-level-facility health workers, focusing on essential care and referral for advanced diagnosis and treatment.  

- dissemination of information on the disease and its prevention through every possible means of communication. The WHO Oral Health Program has developed a manual for oral health through schools (WHO, 2003d), being a component of the WHO Global School Health Initiative (WHO, 2004c) and the World Bank activities (World Bank, 2003).  
- WHO technical support of meetings, at regional or interregional levels, aimed at sharing country experiences in monitoring HIV/AIDS prevention and lifestyle modification through campaigns and community programs  
- assistance to countries in their efforts to develop oral health systems that incorporate oral health care, health promotion, and oral disease prevention aimed at disadvantaged people infected with HIV.

Further information on the WHO Oral Health Program can be found at http://www.who.int/oral_health.

References  

World Health Organization global policy for improvement of oral health – World Health Assembly 2007

Poul Erik Petersen
World Health Organization
Geneva, Switzerland

The World Health Organization (WHO) Global Oral Health Programme has worked hard over the past five years to increase the awareness of oral health worldwide as an important component of general health and quality of life. Meanwhile, oral disease is still a major public health problem in high income countries and the burden of oral disease is growing in many low- and middle income countries. In the World Oral Health Report 2003, the WHO Global Oral Health Programme formulated the policies and the necessary actions for the improvement of oral health. The strategy is that oral disease prevention and the promotion of oral health needs to be integrated with chronic disease prevention and general health promotion as the risks to health are linked. The World Health Assembly (WHA) and the Executive Board (EB) are supreme governance bodies of WHO and for the first time in 25 years oral health was subject to discussion by those bodies in 2007. At the EB120 and WHA60, the Member States agreed on an action plan for oral health and integrated disease prevention, thereby confirming the approach of the Oral Health Programme. The policy forms the basis for future development or adjustment of oral health programmes at national level.

Key words: Oral health, general health, WHO, EB120, WHA60

In 2002, the World Health Organization (WHO) Global Oral Health Programme was reoriented according to a new strategy of integration with chronic disease prevention and general health promotion. Chronic diseases, which continue to dominate in middle- and high income countries, are becoming increasingly prevalent in many of the poorest developing countries. They create a double burden on top of the infectious diseases by which these countries continue to be afflicted. A somewhat similar pattern is observed for the unresolved burden of oral disease, as for the major chronic diseases, socio-environmental factors are distal causes of oral disease, moreover, a core group of modifiable risk factors is common to many chronic diseases and injuries, and most oral diseases. These common risk factors are however preventable as they relate to lifestyles, such as dietary habits, use of tobacco and excessive consumption of alcohol, and the standard of hygiene.

The objectives of the WHO Global Oral Health Programme, one of the technical programmes within the Department of Chronic Disease and Health Promotion, imply that greater emphasis is put on developing global policies based on common risk factors approaches and which are coordinated more effectively with other programmes in public health. The policy of the WHO Global Oral Health Programme emphasises that oral health is integral and essential to general health, and that oral health is a determinant factor for quality of life. The policy is detailed in the World Oral Health Report 2003. The report provides a comprehensive analysis of the global burden of oral disease and additional information of oral health is further described in a Special Theme of the Bulletin of the World Health Organization, September 2005.

WHO priority action areas for the improvement of oral health worldwide are:

- Effective use of fluoride
- Healthy diet and nutrition
- Tobacco control

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Major actions undertaken by the WHO Global Oral Health Programme are detailed in the references given and further information is available from the WHO website www.who.int/oral_health. Elements of the global priorities are also part of the activities undertaken by the oral health programmes of WHO Regional Offices. The Office for the Americas (http://www.paho.org), 10-year Regional Plan on Oral Health/CE138/14) and the Office for Africa (http://www.afro.who.int/oralhealth) have distinct oral health programmes whereas the four other regional offices incorporate oral health into programmes for prevention of chronic disease.

Some activities have been carried out in collaboration with the 32 WHO Collaborating Centres in Oral Health, the two non-governmental Organizations in official relationship with WHO, i.e. Federation Dentaire Internationale/World Dental Federation, and International Association for Dental Research (IADR), or other Organizations such as Aide Odontologique Internationale working for oral health. Several WHO co-sponsored meetings have contributed to sharing of experiences within the oral health community and dissemination of essential messages to the general public, e.g. the WHO/FDI/IADR Global Consultation on use of fluoride for oral health 2006; FDI/WHO/IADR fluoride consultation for China and South-East Asia 2007; WHO/IADR symposium on diet and nutrition 2005; Global conference on tobacco or health 2003; Health Promoting Schools meetings in Thailand, China and India 2003-5; IADR/WHO 5th global workshop on HIV/AIDS in oral health 2004; WHO/IADR symposium on oral health in elderly; WHO/IADR meeting on oral health in Africa and the Middle-East 2004; WHO/FDI meeting on planning of oral health in Africa 2004; WHO/IADR/BASCD meeting on preventive dentistry 2005, and the WHO/AAPD meeting on preventive dentistry in Asia.

The WHO Global Oral Health Programme works from the principles of the Ottawa Charter for Health Promotion\textsuperscript{31}. As underlined by the most recent Bangkok Charter for Health Promotion\textsuperscript{32}, the promotion of health and disease prevention both have established repertoires of evidence-based strategies which need to be fully utilised, especially for low- and middle income countries. The Liverpool Declaration\textsuperscript{33} is an oral health follow-up of the Bangkok Charter, which provides information about the necessary actions to be undertaken by countries for the improvement of oral health.

Progress towards a healthier world requires strong political action, broad participation and sustained advocacy. The WHO Oral Health Programme has worked hard over the years to put oral health high on the health agenda of policy and decision makers worldwide. Recently, the WHO was given the mandate for strengthening the work for oral health by its two governing bodies, i.e. the Executive Board, and the World Health Assembly. The WHO statement will be an impetus for countries to develop or adjust national oral health programmes, and the policy is a strong support to the global actions carried out by the WHO Oral Health Programme.

**WHO governance**

The World Health Assembly is the supreme decision-making body for WHO. It meets each year in May in Geneva, and is attended by delegations from all 193 Member States. The Executive Board is composed of 34 members technically qualified in the field of health. The main Board meeting, at which the agenda for the forthcoming Health Assembly is agreed upon and resolutions are adopted for forwarding to the Health Assembly, is held in January.

In January 2007, the Executive Board at its 120th session discussed the subject of oral health on the basis of the report prepared by the WHO Oral Health Programme\textsuperscript{34}, and the Board subsequently considered a related draft resolution (EB120.R5).

Below is the WHO Oral Health Programme’s contribution to the Sixtieth World Health Assembly held from 14-22 May 2007 which is entitled ‘Oral health: action plan for promotion and integrated disease prevention’, and the subsequent final Resolution WHA60.17\textsuperscript{35}, as confirmed by the Member States.

**Oral health: action plan for promotion and integrated disease prevention - Report by the WHO Secretariat**

Oral disease, such as dental caries, periodontal disease, tooth loss, oral mucosal lesions, oropharyngeal cancers, oral manifestations of HIV/AIDS, necrotising ulcerative stomatitis (noma), and orodental trauma, is a serious public-health problem. Its impact on individuals and communities in terms of pain and suffering, impairment of function and reduced quality of life, is considerable. Globally, the greatest burden of oral diseases lies on disadvantaged and poor populations. The current pattern of oral disease reflects distinct risk profiles across countries related to living conditions, behavioural and environmental factors, oral health systems and implementation of schemes to prevent oral disease. In several high-income countries with preventive oral care programmes prevalence of dental caries in children and tooth loss among adults has dropped. Globally, the
burden of oral disease is particularly high among older people and has a negative effect on their quality of life. In most low- and middle-income countries, the general population does not benefit from systematic oral health care, nor have preventive programmes been established. In some countries the incidence of dental caries has increased over recent years and may further increase as a result of the growing consumption of sugars and inadequate exposure to fluorides.

Tobacco-related oral diseases are currently prevalent in several high-income countries. With the growing consumption of tobacco in many low- and middle-income countries, the risk of periodontal disease, tooth loss and oral-cavity cancer is likely to increase. Moreover, periodontal disease and tooth loss are linked to chronic diseases such as diabetes mellitus; the growing incidence of diabetes in several countries may therefore have a negative impact on oral health. People living with HIV/AIDS suffer from specific oral disease; HIV infection has a negative effect on oral health and quality of life because of, for example, pain, dry mouth and difficulty in chewing, swallowing and tasting food.

Noma, a debilitating orofacial gangrene, is an important contributor to the disease burden in certain low- and middle-income countries, particularly in Africa and Asia; the key risk factors are poverty, severe malnutrition, unsafe drinking water, deplorable sanitary practices and such infectious diseases as measles, malaria, and HIV/AIDS.

Oral disease is the fourth most expensive disease to treat. In high-income countries, the burden of oral disease has been tackled through the establishment of advanced oral-health services which offer primarily treatment to patients. Most systems are based on demand for care provided by private dental practitioners, although some high-income countries have organised public oral-health systems. In most low- and middle-income countries, investment in oral health care is low and resources are primarily allocated to emergency oral care and pain relief.

Most oral diseases and chronic diseases have common risk factors. As is the case for major chronic diseases, oral diseases are linked to unhealthy environments and behaviours, particularly widespread use of tobacco and excessive consumption of alcohol or sugar. In addition to healthy behaviour, promotion of oral health depends on clean water, adequate sanitation, proper oral hygiene and appropriate exposure to fluoride. National health programmes that include health promotion and measures at individual, professional and community levels are cost-effective in preventing oral diseases.

**Framing policies and strategies for oral health**

Promotion of oral health is a cost-effective strategy to reduce the burden of oral disease and maintain oral health and quality of life. It is also an integral part of health promotion in general, as oral health is a determinant of general health and quality of life.

One of the main lines of WHO’s global strategy for the prevention and control of chronic non-communicable diseases is to reduce the level of exposure to major risk factors. Prevention of oral disease needs to be integrated with that of chronic diseases on the basis of common risk factors.

Some high-income countries have built national capacities in oral-health promotion and oral-disease prevention over the past decades, mostly as isolated components of national health programmes. A number of low- and middle-income countries do not yet have policies on, or financial and human resources for, sustainable, effective oral-health programmes to counter risks and their underlying determinants.

To strengthen the formulation or adjustment of policies and strategies for oral health and its integration in national and community health programmes, particular emphasis should be laid on the following elements:

- Promotion of a healthy diet, particularly lower consumption of sugars and increased consumption of fruits and vegetables, in accordance with WHO’s Global Strategy on Diet, Physical Activity and Health, and reduction of malnutrition.

- Prevention of oral and other diseases related to tobacco use (smoking and use of smokeless tobacco), by involving oral-health professionals in tobacco cessation programmes and discouraging children and young people from adopting the tobacco habit.

- Provision of access to clean drinking water, general hygiene and better sanitation for proper oral hygiene.

- Establishment of national plans for use of fluoride, based on appropriate programmes for automatic administration of fluoride through drinking-water, salt, or milk, or topical use of fluoride such as affordable fluoride toothpaste. Salt fluoridation programmes should be linked to iodisation schemes.

- Prevention of oral-cavity cancer and oral pre-cancer by involving oral health professionals or specially trained primary health-care workers in screening, early diagnosis and referral for care, and appropriate interventions on the risks of tobacco use and excessive consumption of alcohol.

- Strengthening of management of HIV/AIDS through oral-health professional screening for HIV/AIDS-related oral disease, early diagnosis, prevention and treatment, with emphasis on pain relief and improved quality of life and on reduction of the double burden of oral disease and HIV infection in low- and middle-income countries.
• Building of capacity in oral-health systems oriented to disease prevention and primary health care, with special emphasis on meeting the needs of disadvantaged and poor populations. Oral-health services should be set up, ranging from prevention, early diagnosis and intervention to provision of treatment and rehabilitation, and the management of oral health problems of the population according to needs and to resources available. In countries with critical shortages of oral-health personnel, essential care may be provided by specially trained primary health-care workers.

• Promotion of oral health in schools, aiming at developing healthy lifestyles and self-care practices in children and young people. An integrated approach that combines school health policy, skills-based health education, a health-supportive school environment and school health services can tackle major common risk factors and contribute to effective control of oral disease.

• Promotion of oral health among older people, aiming at advancing oral health, general health and well-being into old age through a life-course perspective in health promotion, integrated disease prevention and emphasis on age-friendly primary health care.

• Development of oral-health information systems as an integral part of national surveillance of oral health and risk factors, in order to provide evidence for oral health policy and practice, formulation of goals and targets, and measurement of progress in public health. Instruments have been designed in the framework of the WHO Global InfoBase and the WHO STEPSwise approach to surveillance (STEPS).

• Promotion of research in oral health, aimed at bridging gaps in research between low- and middle-income, and high-income countries, conduct of operational research, and translation of knowledge about oral-health promotion and disease prevention into public-health action programmes.

Future action

Working with other international entities involved in oral health, WHO will continue to provide technical support for, and guidance on, the design, implementation and evaluation of evidence-based community demonstration projects worldwide, contribute to sharing of experiences among countries and disseminate lessons learnt through the publication of guidelines. Its expanded evidence base provides a basis for oral-health policies and for investigating the cost and effectiveness of national and community oral health interventions. WHO will also offer technical advice on establishment of integrated oral-health surveillance systems, based on the WHO Global InfoBase and the STEPS methodology. It will also further expand its work with the WHO collaborating centres on oral health and nongovernmental organizations, including the FDI World Dental Federation and the International Association for Dental Research.

In order to respond to the many global changes and trends that directly or indirectly affect oral health and well-being, WHO will further expand its interaction and partnership with other international entities involved in oral health and the private sector within the framework of its overall leadership in health promotion and integrated disease prevention.

Resolution

SIXTIETH WORLD HEALTH ASSEMBLY WHA60.17

Oral health: action plan for promotion and integrated disease prevention

The Sixtieth World Health Assembly,

Recalling resolutions WHA22.30, WHA28.64 and WHA31.50 on fluoridation and dental health, WHA36.14 on oral health in the strategy for health for all, WHA42.39 on oral health; WHA56.1 and WHA59.17 on the WHO Framework Convention on Tobacco Control; WHA58.22 on cancer prevention and control; WHA57.14 on scaling up treatment and care within a coordinated and comprehensive response to HIV/AIDS; WHA57.16 on health promotion and healthy lifestyles; WHA57.17 on the Global Strategy on Diet, Physical Activity and Health; WHA58.16 on strengthening active and healthy ageing; WHA51.18 and WHA53.17 on prevention and control of noncommunicable diseases, and WHA58.26 on public-health problems caused by harmful use of alcohol;

Acknowledging the intrinsic link between oral health, general health and quality of life;

Emphasizing the need to incorporate programmes for promotion of oral health and prevention of oral diseases into programmes for the integrated prevention and treatment of chronic diseases;

Aware that the importance of the prevention and control of noncommunicable diseases has been highlighted in the Eleventh General Programme of Work 2006–2015;
Appreciating the role that WHO collaborating centres, partners and nongovernmental organizations play in improving oral health globally,

**URGES Member States:**

1. to adopt measures to ensure that oral health is incorporated as appropriate into policies for the integrated prevention and treatment of chronic noncommunicable and communicable diseases, and into maternal and child health policies;

2. to take measures to ensure that evidence-based approaches are used to incorporate oral health into national policies as appropriate for integrated prevention and control of noncommunicable diseases;

3. to consider mechanisms to provide coverage of the population with essential oral-health care, to incorporate oral health in the framework of enhanced primary health care for chronic noncommunicable diseases, and to promote the availability of oral-health services that should be directed towards disease prevention and health promotion for poor and disadvantaged populations, in collaboration with integrated programmes for the prevention of chronic noncommunicable diseases;

4. for those countries without access to optimal levels of fluoride, and which have not yet established systematic fluoridation programmes, to consider the development and implementation of fluoridation programmes, giving priority to equitable strategies such as the automatic administration of fluoride, for example, in drinking-water, salt or milk, and to the provision of affordable fluoride toothpaste;

5. to take steps to ensure that prevention of oral cancer is an integral part of national cancer-control programmes, and to involve oral-health professionals or primary health care personnel with relevant training in oral health in detection, early diagnosis and treatment;

6. to take steps to ensure the prevention of oral disease associated with HIV/AIDS, and the promotion of oral health and quality of life for people living with HIV, involving oral-health professionals or staff who are specially trained in primary health care, and applying primary oral-health care where possible;

7. to develop and implement the promotion of oral health and prevention of oral disease for preschool and school children as part of activities in health-promoting schools;

8. to scale up capacity to produce oral-health personnel, including dental hygienists, nurses and auxiliaries, providing for equitable distribution of these auxiliaries to the primary-care level, and ensuring proper service backup by dentists through appropriate referral systems;

9. to develop and implement, in countries affected by noma, national programmes to control the disease within national programmes for the integrated management of childhood illness, maternal care and reduction of malnutrition and poverty, in line with internationally agreed health-related development goals, including those contained in the Millennium Declaration;

10. to incorporate an oral-health information system into health surveillance plans so that oral-health objectives are in keeping with international standards, and to evaluate progress in promoting oral health;

11. to strengthen oral-health research and use evidence-based oral-health promotion and disease prevention in order to consolidate and adapt oral-health programmes, and to encourage the intercountry exchange of reliable knowledge and experience of community oral-health programmes;

12. to address human resources and workforce planning for oral health as part of every national plan for health;

13. to increase, as appropriate, the budgetary provisions dedicated to the prevention and control of oral and craniofacial diseases and conditions;

14. to strengthen partnerships and shared responsibility among stakeholders in order to maximize resources in support of national oral health programmes;

**REQUESTS the Director-General:**

1. to raise awareness of the global challenges to improving oral health, and the specific and unique needs of low- and middle-income countries and of poor and disadvantaged population groups;

2. to ensure that the Organization, at global and regional levels, provides advice and technical support, on request, to Member States for the development and implementation of oral-health programmes within integrated approaches to monitoring, prevention and management of chronic noncommunicable diseases;

3. continually to promote international cooperation and interaction with and among all actors concerned with implementation of the oral-health action plan, including WHO collaborating centres for oral health and nongovernmental organizations;

4. to communicate to UNICEF and other organizations of the United Nations system that undertake health-related activities, the importance of integrating oral health into their programmes;

5. to strengthen WHO’s technical leadership in oral health, including increasing, as appropriate, budgetary and human resources at all levels.
Oral health services development and adjustment

The WHO Global Oral Health Programme gives priority to the organization of oral health services that matches the needs of the population. In several industrialized Western countries, oral health services are made available to the population, either based on public or private systems. Meanwhile, people in deprived communities, homebound and disabled individuals, old-age persons, and certain ethnic minorities are not sufficiently covered by oral health care. Social inequality in oral health status and use of services is somewhat universal, even in the Nordic countries with public responsibility in financing and delivery of oral health care remarkable differences are observed by social class. Outreach services may be necessary to tackle the burden of poor oral health of people with limited resources and lack of tradition of regular oral health care.

By and large, the industrialized countries show appropriate numbers of dentists whereas there is shortage of dental ancillary personnel to carry out preventive care and health promotion. The problem of production of inappropriate types and numbers of oral health professionals is still being faced by most of the industrialised countries. In some countries, the introduction of ancillary personnel has been delayed. It has been reported, particularly in countries where over-production exists and the oral health of the population has improved, that duties which traditionally have been performed by assisting personnel are now being carried out by dentists themselves.

While there is a need for adjustment of oral health services in high-income countries, services are often not available or accessible for the general population in the majority of developing countries. This is particularly the case for Latin America, Asia and the poor countries of Africa. There is significant lack of oral health personnel, the WHO Global Oral Health Programme has drawn a global map demonstrating that Sub-Saharan countries have a critical shortage of oral manpower. Moreover, cost of oral health services is high, the use of services is often prompted by symptoms and services are mostly oriented towards relief of pain. Oral health care is generally provided by hospitals located in urban centres whereas limited care is offered in rural areas. In the majority of countries in Africa and Asia little attention is given to oral health of people living with HIV/AIDS who are less aware of the oral manifestations of infection than the general symptoms.

The lack of oral health services highly reflects the low priority to oral health by policy makers and decision makers in these countries and oral health staff or chief dental officers are most often not available within ministries of health. In the future, strong emphasis should be given to the effective implementation of integrated primary oral health care according to the WHO Primary Health Care concept in 1979.

Worldwide, the priority given to prevention of oral disease and health promotion is far too low. In 1986, the so-called Ottawa Charter on Health Promotion emphasised that health services should be effectively oriented towards prevention and health promotion. The need is still high for adjustment of programmes in countries with existing oral health services and for countries in the process of developing oral health programmes strong efforts should be made towards the implementation of prevention and health promotion. For all countries the adjustment or development of national oral health programmes should incorporate systematic activities towards oral cavity cancer and the oral manifestation of HIV/AIDS, including early diagnosis and referral for specialist care.

The 2005 Bangkok Charter for Health Promotion in a Globalized World states that the evidence is available on the effectiveness of chronic disease prevention and health promotion, and the challenge for national health authorities and health care providers is urgently to translate this knowledge into practice for the benefit of the disadvantaged people or nations. Health services should be financially fair and be based on outreach principles in order to cover the whole population. The Liverpool Charter on Oral Health Promotion gives direction to oral health planners and oral health providers for implementation of appropriate oral health programmes based on the wealth of evidence on oral disease prevention and oral health promotion. As underlined by the WHO Global Oral Health Programme, it is most relevant to ensure that such programmes are not isolated activities but integrated with national health programmes. WHO has designed an operational plan for oral health globally and the WHO Global Oral Health Programme is prepared to assist the national health authorities in this effort and in partnership with non-governmental Organizations.

References


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