Lessons in Preventive Cardiology from The Honolulu Heart Program

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NI-HON-SAN


Its goal was to confirm the reported mortality gradient of increasing CHD among Japanese men in Japan, Hawaii, and California and the opposite gradient for stroke mortality.
The **NI-HON-SAN** Study

NIHON

HON OLULU

NI PPON

SAN FRANCISCO
The *NI-HON-SAN* Study

1965-1970

JAPAN    HAWAII    CALIFORNIA

2,141    8,006    1,844

( MEN 45 to 69 YEARS OLD )
Features of the HHP

- Designed after the Framingham Study.
- Prospective observational study.
- Men of Japanese ancestry.
- Resident on the island of Oahu.
- Born from 1900 to 1919.
- Age range 45 to 68 at study entry.
- Entry exam from 1965 to 1968 with repeat exams over the course of follow-up.
- Primary endpoints include CHD, stroke and mortality.
Age-adjusted mean body weight at baseline examination of the NI-HON-SAN Study

Japan: 55.1 kg
Hawaii: 63.3 kg
California: 65.8 kg

Hawaii Medical Journal; Vol.44, No. 8-August 1985
Age-adjusted percent with hypertension (≥ 160/95 mmHg) at baseline examination of the NI-HON-SAN Study
Age-adjusted percent with hypercholesterolemia (≥ 260 mg/dl) at baseline examination of the NI-HON-SAN Study

Japan: 3.2%
Hawaii: 12.4%
California: 16.3%

Hypercholesterolemia (>260 mg/dl)

Hawaii Medical Journal; Vol.44, No. 8-August 1985
Age-adjusted percent with hypertriglyceridemia ($\geq 280$) at baseline examination of the NI-HON-SAN Study

Japan: 6.1
Hawaii: 24.6
California: 25.2

Triglycerides $\geq 280$ mg/dl*

*Nonfasting values

Hawaii Medical Journal; Vol.44, No. 8-August 1985
Age-adjusted mean serum glucose (mg/dl)* at baseline examination of the NI-HON-SAN Study

*One-hour value after ingestion of 50g glucose

Hawaii Medical Journal; Vol.44, No. 8-August 1985
Age-adjusted percent with hyperglycemia (glucose ≥ 200) at baseline examination of the NI-HON-SAN Study

Japan: 11.3%
Hawaii: 20.2%
California: 19.2%

Glucose ≥ 200 mg/dl

Hawaii Medical Journal; Vol.44, No. 8-August 1985
Mean values of alcohol intake at baseline examination of the NI-HON-SAN study

- Japan: 28
- Hawaii: 13
- California: 9

Alcohol (gm/day)
Percent of calories from fat at baseline examination of the NI-HON-SAN study

- Japan: 15.1%
- Hawaii: 33.2%
- California: 37.6%

Percent Calories, Fat
Percent of calories from carbohydrates at baseline examination of the NI-HON-SAN study.
Comparative stroke rates in the NI-HON-SAN Study

Age-adjusted Prevalence Rates/1,000

- Japan: 42.5
- Hawaii: 15
- California: 13

Stroke (Verified by a Physician)
Comparative rates of CHD in the NI-HON-SAN Study

Age-adjusted Prevalence Rates/1,000

- Japan: 7.3
- Hawaii: 13.2
- California: 31.4

History of MI
Diabetes and Cardiovascular Diseases
Introduction

- Changes in human lifestyle and behavior in the last century has lead to a dramatic increase in the incidence of diabetes around the world.
- There is a current epidemic of diabetes type 2 caused by the combination of genetic factors and environmental factors such as sedentary lifestyle, overly rich nutrition and obesity.
Number of People with Diabetes (in millions 2000 & 2010) and percent increase.

No. of People with Diabetes in millions in 2000 and 2010 and % increase

World
2000: 151 m
2010: 221 m
increase 46%

The Prevalence of Type 2 Diabetes Mellitus among Chinese in Hong Kong, Singapore, Taiwan & Mauritius, compared with that in the People’s Republic of China

Honolulu Heart Program
Background Information

During the baseline examination in 1965, a nonfasting 1-h post-load glucose test was used to screen this population.

Since 1965 men were followed through a comprehensive hospital surveillance system.
## Classification of Subjects by Glucose Tolerance Status

<table>
<thead>
<tr>
<th></th>
<th>Normoglycemia</th>
<th>Glucose Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-Normal</td>
<td>High-Normal</td>
</tr>
<tr>
<td></td>
<td>n=3,795</td>
<td>n=2,719</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Medication for diabetes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1-hr postload glucose, mg/dl</td>
<td>&lt;151</td>
<td>151-224</td>
</tr>
</tbody>
</table>

*J.D. Curb, Circulation Vol 91, No 10 May 15, 1995;*
Age and Risk Factor-adjusted RR of Thromboembolic Stroke by Glucose Tolerance, 1965-1988

* C. Burchfiel; Stroke Vol 25, No 5, May 1994

* C. Burchfiel; Stroke Vol 25, No 5, May 1994
Age and Risk Factor-adjusted RR of Total Stroke by Glucose Tolerance, 1965-1988

* C. Burchfiel; Stroke Vol 25, No 5, May 1994
Age and Risk Factor-adjusted RR of CHD Incidence by Glucose Tolerance

* B.L. Rodriguez; Diabetes Care Vol 22; No 8; 1262-1265, August 1999
Age and Risk Factor-adjusted RR of CHD Mortality by Glucose Tolerance

* B.L. Rodriguez; Diabetes Care Vol 22; No 8; 1262-1265, August 1999
Risk Factor-Adjusted Relative Risk of Sudden Death (1 Hr) by Glucose Tolerance Status, 1965 through 1988

*J.D. Curb, Circulation Vol 91, No 10 May 15, 1995;*
Risk Factor-Adjusted Relative Risk of Sudden Death (24 Hr) by Glucose Tolerance Status, 1965 through 1988

*J.D. Curb, Circulation Vol 91, No 10 May 15, 1995;
Age and Risk Factor-adjusted RR of Total Mortality by Glucose Tolerance

* B.L. Rodriguez; Diabetes Care Vol 22; No 8; 1262-1265, August 1999
Fourth Examination

In 1991-1993, the Fourth Examination was undertaken in a collaborative effort of the National Heart Lung and Blood Institute and the National Institute on Aging to examine all HHP survivors to study dementia, cardiovascular diseases, diabetes and other diseases that affect the elderly.
Research Design

- Exams given from 1991 to 1993 in the Honolulu Heart Program were used as baseline for these analyses.
- Subjects were 71-93 years old.
- Subjects were followed for total and cardiovascular disease mortality for up to 7 years.
33% of US population ≥ 75 years old has dm or IGT

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>IGT</th>
<th>Unknown Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>738</td>
<td>734</td>
<td>428</td>
<td>652</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3</td>
<td>23.9*</td>
<td>24.1*</td>
<td>23.8*</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.94</td>
<td>0.94*</td>
<td>0.95*</td>
<td>0.95*</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>130</td>
<td>151*</td>
<td>163*</td>
<td>159*</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>53</td>
<td>51*</td>
<td>49*</td>
<td>48*</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>12</td>
<td>14</td>
<td>16</td>
<td>29*</td>
</tr>
<tr>
<td>2-h Insulin (µU/ml)</td>
<td>89</td>
<td>140*</td>
<td>140*</td>
<td>94</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>101</td>
<td>105*</td>
<td>120*</td>
<td>146*</td>
</tr>
<tr>
<td>2-h glucose (mg/dl)</td>
<td>112</td>
<td>167*</td>
<td>254*</td>
<td>285*</td>
</tr>
</tbody>
</table>

*B.L. Rodriguez; Diabetes Care Vol 19, No 6, June 1996.
Age-adjusted Mean Levels and Percentages for Selected CVD Risk Factors by Glucose Tolerance Status

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Normal</th>
<th>IGT</th>
<th>Unknown Diabetes</th>
<th>Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension ≥ 140/90 or medications (%)</td>
<td>68</td>
<td>77*</td>
<td>80*</td>
<td>77*</td>
</tr>
<tr>
<td>Physical activity index</td>
<td>32</td>
<td>31</td>
<td>31</td>
<td>30*</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>300</td>
<td>303</td>
<td>310*</td>
<td>316*</td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>191</td>
<td>193</td>
<td>193</td>
<td>187*</td>
</tr>
<tr>
<td>Current smoking (cigarettes/day)</td>
<td>12</td>
<td>16</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Current drinking (oz/month)</td>
<td>20</td>
<td>22</td>
<td>25</td>
<td>19</td>
</tr>
</tbody>
</table>

*P<0.05, normal group as reference.

*B.L. Rodriguez; Diabetes Care Vol 19, No 6, June 1996.
Glucose metabolism status in subjects not taking medication for diabetes (1991-93)

<table>
<thead>
<tr>
<th>ADA</th>
<th>WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal (n=678)</td>
</tr>
<tr>
<td>Normal (n=1,404)</td>
<td>678</td>
</tr>
<tr>
<td>Impaired fasting glucose (n=455)</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes (n=175)</td>
<td>0</td>
</tr>
<tr>
<td>Percentage</td>
<td>33</td>
</tr>
</tbody>
</table>

(n=2,034)

*B.L. Rodriguez; Diabetes Care Vol 25, No 6, June 2002.*
Age-adjusted Mortality Rates by Glucose Levels

* total number=2034

* B.L. Rodriguez; Diabetes Care Vol 25, No 6, June 2002.
### Risk Factor* Adjusted Relative Risk for CVD Mortality by Glucose Metabolism Status

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>WHO</th>
<th>2-Hr Only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IGT/IFG</strong></td>
<td>0.88 (0.52-1.47)</td>
<td>1.33 (0.81-2.20)</td>
<td>1.10 (0.68-1.78)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>2.03 (1.14-3.61) §</td>
<td>1.81 (1.07-3.08) §</td>
<td>1.59 (0.97-2.61)</td>
</tr>
</tbody>
</table>

* § P<0.05

A total of 358 death during follow-up, including 103 cardiovascular deaths (n=2,034)

*B.L. Rodriguez; Diabetes Care Vol 25, No 6, June 2002.*
<table>
<thead>
<tr>
<th>Risk Factor*</th>
<th>Adjusted Relative Risk for Total Mortality by Glucose Metabolism Status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADA</td>
</tr>
<tr>
<td>IGT/IFG</td>
<td>1.12 (0.80-1.45)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.75 (1.24-2.47) §</td>
</tr>
</tbody>
</table>

• § P<0.05

• A total of 358 death during follow-up, including 103 cardiovascular deaths (n=2,034)

*B.L. Rodriguez; Diabetes Care Vol 25, No 6, June 2002.
Relative Risk of **CVD Mortality** at 80\textsuperscript{th} versus 20\textsuperscript{th} percentile for fasting and 2 hr postload Glucose

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Age-adjusted</th>
<th>Risk Factor Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>0.97 (0.75-1.25)</td>
<td>1.05 (0.81-1.37)</td>
</tr>
<tr>
<td>2-Hr</td>
<td>1.48 (1.04-2.10)†</td>
<td>1.43 (1.01-2.03) †</td>
</tr>
</tbody>
</table>

* N= 103. Adjusted for age, BMI, waist-to-hip ratio, physical activity, hypertension, triglycerides, HDL cholesterol, fibrinogen, and other glucose measurements.

* B.L. Rodriguez; *Diabetes Care* Vol 25, No 6, June 2002.
Relative Risk of Total Mortality at 80\textsuperscript{th} versus 20\textsuperscript{th} percentile for fasting and 2 hr postload Glucose

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Age-adjusted</th>
<th>Risk Factor Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>0.91 (0.78-1.05)</td>
<td>0.98 (0.85-1.13)</td>
</tr>
<tr>
<td>2-Hr</td>
<td>1.50 (1.24-1.81)†</td>
<td>1.45 (1.20-1.75) †</td>
</tr>
</tbody>
</table>

* N= 358. Adjusted for age, BMI, waist-to-hip ratio, physical activity, hypertension, triglycerides, HDL cholesterol, fibrinogen, and other glucose measurements.

*B.L. Rodriguez; Diabetes Care Vol 25, No 6, June 2002
Summary

- Glucose intolerance and diabetes in middle age are associated with an increased risk of total and thromboembolic stroke, CHD incidence and mortality, sudden death and total mortality.

- Hemorrhagic stroke is not associated with diabetes in this population.
Summary

- Glucose metabolism abnormalities are highly prevalent among Japanese American elderly men

- Individuals with IGT or diabetes have significantly more adverse risk factors compared to normal subjects
Summary

The ADA classification of diabetes results in 66% fewer subjects with unrecognized or untreated diabetes and more than twice the number of normal subjects in this elderly population.

IGT and IFG were not associated with total or CVD mortality in this elderly group.
Summary

However, diabetes is associated with an increased risk of total and CVD mortality.

Similar RR were observed regardless of which classification was used. However, the absolute number of persons who would be identified as being at high risk are vastly different.
Summary

- The 2 hr measurement is a superior predictor of total and CVD mortality compared with fasting glucose alone.

- The difference in the results (categorical vs. continuous analyses) suggests that the cutoff points should be re-evaluated.
Summary

- Diabetes is a major risk factor for cardiovascular diseases and mortality.

- Interventions to prevent and treat diabetes and associated CVD risk factors are important strategies in the prevention of cardiovascular diseases.
Honolulu Heart Program

- The Honolulu Heart Program has contributed substantially to our knowledge on cardiovascular disease epidemiology.

- The HHP has resulted in more than 450 publications to date.

- Much of this knowledge can be extrapolated to other populations.

- Studies in the HHP offspring have been initiated.
Aloha