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**PERSPECTIVES ON ABDOMINAL ADIPOSITY AND OBESITY-RELATED DISEASES FROM THE SEATTLE JAPANESE AMERICAN COMMUNITY DIABETES STUDY**

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To receive the Per Björntorp/Jean Vague Lecture Award is a tremendous honour and to present the lecture on behalf of my colleagues in Seattle is a great privilege. What I will do is describe the history behind our research, how the writings of both Per Björntorp and Jean Vague as well as others influenced the direction of our research, and some of our key findings regarding intra-abdominal (visceral) adiposity and obesity-related diseases.

**Key Points**

The Seattle Japanese American Community Diabetes Study showed in Japanese Americans:

- A high prevalence of diabetes;
- Intra-abdominal (visceral) adiposity to be a key risk factor in obesity-related diseases;
- Lifestyle (diet and physical activity) could favourably affect intra-abdominal adiposity and risk for diabetes (and other obesity-related diseases);
- Lifestyle modification may be able to prevent diabetes (and other obesity-related diseases?).

The Seattle Japanese American Community Diabetes Study enrolled the first participant in 1983 and ended in 2001 when I left the University of Washington for retirement in Kailua Kona, Hawaii. A total of 658 men and women were studied over a 10-year follow-up interval with 75.5% of participants returning for follow-up. Among the results of this study was the finding that intra-abdominal adiposity plays a crucial role in the etiopathogenesis of obesity-related diseases.

In 1971, at the annual meeting of the American Diabetes Association in San Francisco a Japanese diabetologist said to me: “Diabetes rates are quite low in Japan when compared to your country. There are many Japanese people who were born and grew up in the United States. How do these Japanese Americans compare to our Japanese?” At that time I was about to complete a fellowship in endocrinology at the University of Washington. My research was conducted entirely at the lab bench, using cultures of islet cells, fibroblasts, and later on, adipose cells to examine islet hormone production and insulin action. I had funding for this research from the National Institutes of Health and the

American Diabetes Association and had no reason to change the direction of my career except that I kept thinking about this earlier conversation. In 1977, I went to Index Medicus (there was no PubMed at that time) and came across a paper authored by Sloan [1] and published in JAMA in 1963. Sloan reported diabetes rates to be almost 3-fold higher in Japanese than in Caucasians living on the island of Oahu in Hawaii. This difference was very striking and unexpected based upon reports of low diabetes rates in Japan. This piqued my interest in the etiology and pathogenesis of type 2 diabetes in Japanese Americans and in retrospect probably marked the turning point in the direction of my academic career.

I had no prior experience in the field of clinical epidemiology. But I was keenly interested in learning more about diabetes in Japanese Americans. In order to obtain research funding to follow through on this interest, I had to demonstrate both the capability of leading a clinical epidemiologic study and of obtaining some preliminary data. To accomplish this, we obtained funding for a pilot study from both the American Diabetes Association and the Kroc Foundation as well as funding from the Japan Society for the Promotion of Science to support a sabbatical at the University of Tokyo. We conducted the pilot study from 1978 to 1980 and I was on sabbatical from 1979 to 1980. By comparing diabetic Japanese men in Tokyo and Seattle and diabetic Caucasian men in Seattle, we found that Japanese Americans were fatter than native Japanese but leaner than Caucasians, Japanese Americans and Japanese consumed similar amounts of food and less than Caucasians but Japanese Americans took in more total fat and less carbohydrates than Japanese, and Japanese Americans consumed as much fat percentage as Caucasians [2, 3]. These observations raised several questions, including: 1) Is there anything else besides body size that is important? 2) How do diabetes rates in Japanese Americans compare to rates in Japanese? 3) How is lifestyle related to the etiopathogenesis of type 2 diabetes?

Although it seemed that “fatness” was important, we wondered whether there might be something else that was important. It was while we were preparing our National Institutes of Health grant application that we became aware of several key papers that greatly influenced us: Vague’s publication [4] in the American Journal of Clinical Nutrition in 1956, “The Degree of Masculine Differentiation of Obesities” in which he described the characteristics of gynoid and android obesity; another by Kissebah et al. [5] in the Journal of Clinical Endocrinology and Metabolism in 1982, “Relation of Body Fat Distribution to Metabolic Complications of Obesity”; and a third by Krotkiewski et al. [6] (including Björntorp) in Journal of Clinical Investigation in 1983, “Impact of Obesity on Metabolism in Men and Women”. In addition, we also became aware of the application of computed tomography (CT) to assess intra-abdominal body fat from a report by Borkan et al. [7] presented initially at a scientific meeting and subsequently published in the American Journal of Clinical Nutrition in 1982, “Assessment of Abdominal Fat Content by Computed Tomography”. This was followed in 1983 by a paper by Tokunaga et al. [8] from Japan in the International Journal of Obesity, “A Novel Technique for the Determination of Body Fat by Computed Tomography”. Based on all of these reports, we used both anthropometry and CT to assess body fat distribution in our Japanese-American participants.

When we performed an oral glucose tolerance test in diabetic men in Tokyo and Seattle, men in Seattle had much higher plasma insulin levels than Tokyo men despite similar glucose levels, suggesting that Seattle men were more insulin resistant [9]. After adjusting for the higher body mass index (BMI) in Seattle, fasting insulin remained significantly greater in Seattle. Although body fat distribution was not assessed in Tokyo, it became quickly apparent in Seattle that diabetic men tended to have higher amounts of intra-abdominal fat than normal men (Figure 1). This was subsequently confirmed in Japanese-American women as well and validated the importance of this measurement in this population.

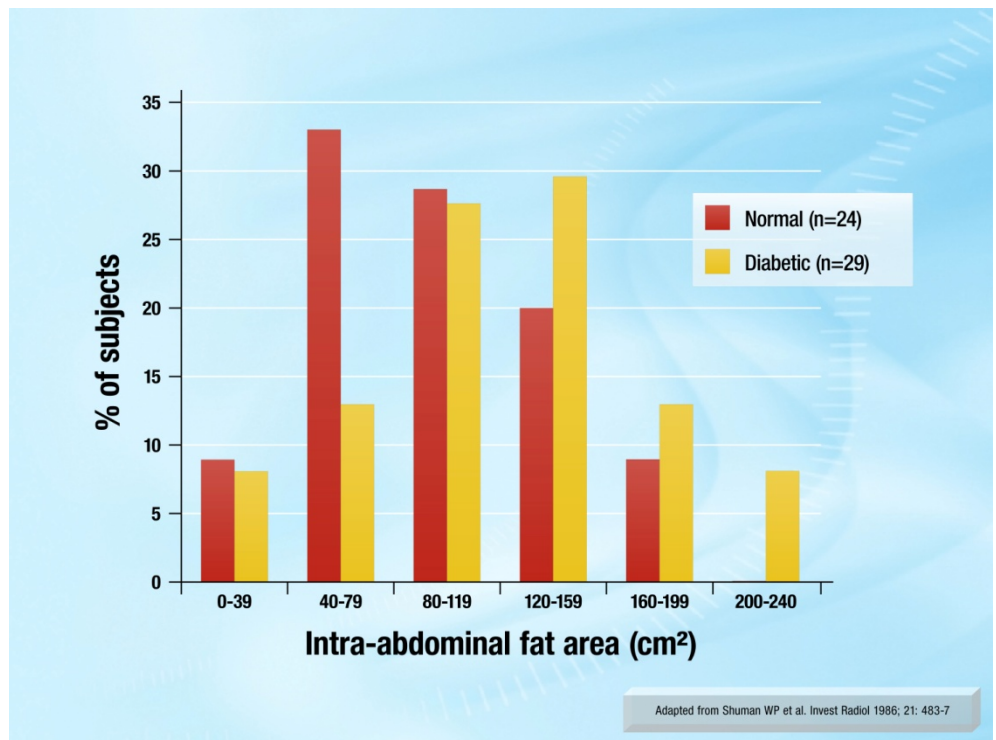


Figure 1: Distribution of intra-abdominal fat area: normal and diabetic Japanese-American men

Over the course of the 10-year follow-up of our study participants, we examined the incidence of obesity-related diseases and found that intra-abdominal adiposity was an independent precursor to coronary heart disease, hypertension, diabetes, impaired glucose tolerance, and metabolic syndrome whereas other measurements of body size and shape (e.g., BMI, total CT fat area, subcutaneous fat area, waist circumference) did not independently predict these diseases when intra-abdominal fat area was in the analysis [10-15]. All of these have also been reported to be associated with insulin resistance. We therefore asked: “Does intra-abdominal adiposity predict insulin resistance?” Shown in the Table are results from a model that included both intra-abdominal fat and abdominal subcutaneous fat in predicting future insulin resistance. Other models substituting total subcutaneous fat area, total fat area, BMI, and waist circumference also showed that intra-abdominal fat was an independent predictor of insulin resistance [16].

Independent variables (baseline)	Log <sub>e</sub> (HOMA-IR)	
	β	P
<b>Intra-abdominal fat area</b>	0.0631	<b>&lt;0.001</b>
Abdominal subcutaneous fat area	-0.0003	0.554
<b>HOMA-IR *</b>	0.1327	<b>&lt;0.001</b>
Incremental insulin response	0.0003	0.665
2-hour plasma glucose	0.0002	0.791
Age	-0.0033	0.151
Gender	-0.0692	0.227
<b>Model R<sup>2</sup></b>	<b>0.362</b>	

\* Similar findings when fasting insulin was substituted for homeostasis model assessment of insulin resistance (HOMA-IR)

Adapted from Hayashi T et al. Diabetes 2008; 57: 1269-75

Table: Multivariate model showing intra-abdominal fat to be an independent predictor of future insulin resistance

We identified a “diabetogenic” lifestyle in Japanese Americans, one that included a diet high in saturated fat content (and lower in carbohydrates) and lower physical activity (lower energy expenditure). This lifestyle was related to greater plasma glucose levels [17]. Moreover, change in intra-abdominal fat appeared to be directly correlated with the amount of daily saturated fat intake. We therefore designed a small randomized clinical trial to examine this further.

Japanese Americans with impaired glucose tolerance were randomized in two groups: 1) a treatment group that was given instruction in aerobic exercise and a diet with saturated fat reduced to 7% of total calories; 2) a comparison group that was given instruction in stretching exercise and a diet with saturated fat reduced to 10% of total calories. Both groups were followed for 24 months, closely for the first 6 months, less closely for the next 6 months, and even less closely for the final 12 months. The treatment group showed significant reduction in BMI (although weight loss was not a goal) and improvement in body fat distribution, glucose levels, and insulin sensitivity, but there was no effect upon β-cell function (Figure 2) [18, 19]. Thus, lifestyle modification may be an effective approach to preventing or delaying type 2 diabetes in at-risk Japanese Americans.

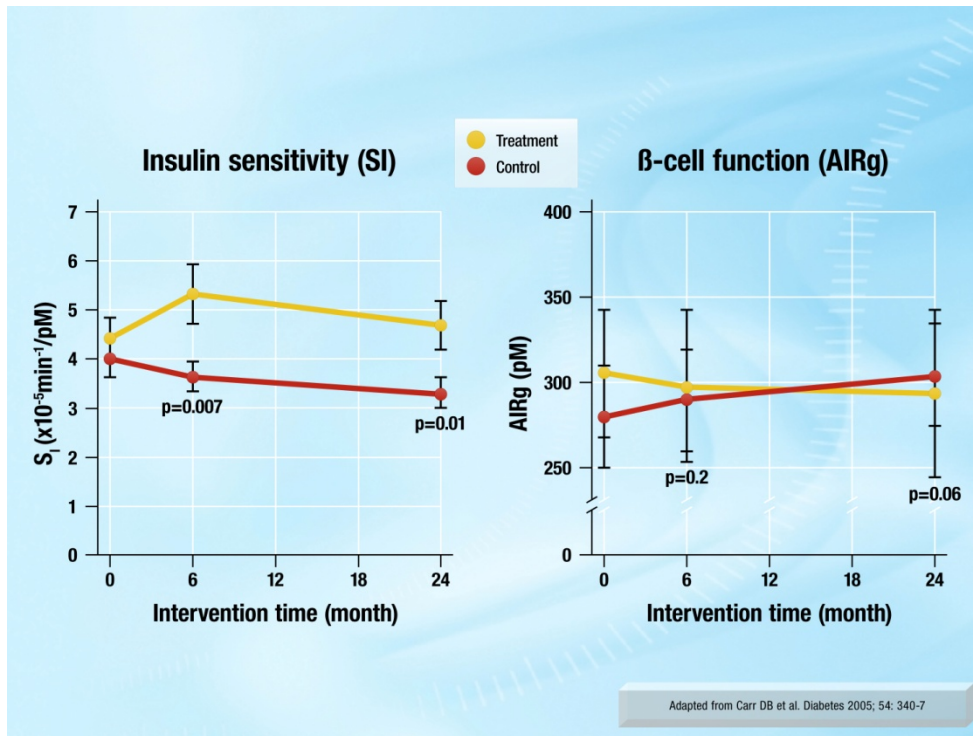


Figure 2: Multiple linear regression analysis of HOMA-IR at follow-up in Japanese Americans

In summary, the Seattle Japanese American Community Diabetes Study showed in Japanese Americans:

- A high prevalence of diabetes;
- Intra-abdominal adiposity to be a key risk factor in obesity-related diseases;
- Lifestyle (diet and physical activity) could favourably affect intra-abdominal adiposity and risk for diabetes (and other obesity-related diseases);
- Lifestyle modification may be able to prevent diabetes (and other obesity-related diseases?).

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