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REVIEW ARTICLE

2015 Yutaka Seino Distinguished Leadership Award Lecture: The Japanese American Community Diabetes Study and the 'canary in the coal mine'

Wilfred Y Fujimoto*

Department of Medicine, University of Washington, Seattle, Washington, USA

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***Correspondence**
Wilfred Y Fujimoto
Tel.: +1-808-325-3194
E-mail address: wilfuji@u.washington.edu

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ABSTRACT

The rising tide of diabetes in Asia has been preceded by high prevalence rates of diabetes among migrant Asian populations in the USA and elsewhere. A 1963 report from Hawaii showed that diabetes was much more prevalent in Japanese Americans than in Caucasians. The Japanese American Community Diabetes Study was begun in Seattle, Washington, to examine why this was the case, and explore the etiology and pathogenesis of type 2 diabetes among Japanese Americans who were Nisei (second generation) and Sansei (third generation) descendants of the original immigrants to the USA from Japan. This research was planned to be a metabolically-based longitudinal epidemiological study that assessed lifestyle factors, insulin sensitivity, insulin secretion and adiposity, including measurements of body fat distribution by anthropometry and computed tomography (CT). An important conclusion from this research was that visceral adiposity was a powerful risk factor for metabolic disease. Our observations suggested that among susceptible Japanese Americans lifestyle led to weight gain, especially in visceral fat depots, that in turn led to decreased insulin sensitivity that unmasked a reduced β-cell reserve, resulting in hyperglycemia and type 2 diabetes. This process can be prevented by dietary and exercise intervention. Thus, the Japanese American population has served as an early warning system for type 2 diabetes in Asians, just as caged canaries were used by coal miners as an early warning system for harmful gases in coal mines.

INTRODUCTION

Coal miners carried caged canaries with them down into mine tunnels in order to detect dangerous gases, such as methane or carbon monoxide (Figure 1). The gases would kill the canary before they could harm the miners, thus providing an early warning system. In retrospect, our study of Japanese Americans in Seattle has served as an early warning system for the diabetes tsunami that has swept through other Asian populations worldwide[1]. My lecture reviewed how my research focus turned to the epidemiology of diabetes in Japanese Americans, and presented some of the history behind and the highlights from this research. An extensive review of this research has been previously published[2].

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> 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?

This was asked of me by a Japanese diabetologist at the annual scientific meeting of the American Diabetes Association in June 1971. Little did I know at that time that my later recollection of this conversation would lead to a major change in the direction of my research career which, at that time, was just beginning at the University of Washington and was entirely at the laboratory bench. Dr Robert Williams, who was head of the Division of Metabolism and Endocrinology, had given me the responsibility of establishing a cell culture laboratory in the Division, and my research was beginning to use cell cultures of islet cells, fibroblasts and adipocytes to examine some of the processes fundamental to an understanding of diabetes[3–

Figure 1 | A caged canary served as an early warning system to miners for the presence of dangerous gases in coal mines.

[12]. Being fully immersed in this research, I did not expect that within 10 years I would become deeply interested in studying culture of another type, lifestyle, in the development of diabetes in Japanese Americans. The lecture that I delivered at the 7th Annual Meeting of the Asian Association for the Study of Diabetes reviewed the history leading up to and some of the highlights from this metabolically-based epidemiological study into the etiology and pathogenesis of type 2 diabetes among Japanese Americans.

In 1963, Sloan published a report from Hawaii showing ethnic prevalence rates for diabetes[13]. In 1958 and 1959, 38,103 'gainfully employed' civilian residents of Oahu were studied. Screening glucose ≥130 mg/dL from finger blood samples obtained at 2–2.5 h after a meal containing at least 50 g of carbohydrate identified those who needed to be retested, and those identified as possibly diabetic were then referred to their physician for confirmation of diabetes. Although the diagnostic criteria for diabetes were quite different from those used today, nevertheless it was abundantly clear from that report that Asians in Hawaii had a much higher prevalence of diabetes than Caucasians (Table 1). Among those who were of single race, Japanese comprised by far the largest number (16,134). This might be the earliest report about ethnic differences in diabetes rates in the USA that included Asians, and suggested to me that Seattle Japanese Americans were likely to also have a high risk of diabetes.

Table 1 | Age-adjusted ethnic prevalence of diabetes mellitus in Hawaii in 1958–1959

Race (single)	Number screened	Diabetes rate (per 1,000 persons)
Caucasian	4,473	7.3
Chinese	3,755	14.6
Filipino	4,321	21.8
Japanese	16,134	20.1
Korean	539	19.7
Hawaiian	626	48.8

PILOT STUDY

Because my laboratory research was well underway by 1978, to learn more about diabetes among Seattle Japanese Americans I successfully applied for funding from the Kroc Foundation and from the American Diabetes Association for a pilot study that would compare diabetic Japanese men in Seattle and Tokyo and diabetic Caucasian men in Seattle. I also took a sabbatical leave at the University of Tokyo in the Third Department of Medicine, which was directed by Professor Kinori Kosaka. Soon after arriving in Tokyo, I had my first meeting with Professor Kosaka, who discussed with me his thoughts about the differences in diabetes between Japan and the USA. The main points of this discussion were: (i) Japanese with diabetes have low blood insulin levels; (ii) Americans with diabetes have high blood insulin levels; (iii) diabetes develops in Japanese because their β-cells are 'weak'; and (iv) diabetes develops in Americans because they are obese and insulin resistant.

The age distribution of Japanese Americans in Seattle is quite interesting and is explained by the immigration history of Japanese from Japan to the USA. Immigration began in the 1800s and continued until 1924 when immigration from Asia to the USA was blocked by the government. This resulted in the age distribution in 1980 shown in Figure 2. This age distribution pattern showed three peaks: the immigrant Issei (aged ≥75 years), their Nisei children (peak at approximately 55 years) and their Sansei grandchildren (peak at approximately 25 years). We chose to include Nisei men for the pilot study. From this pilot study, we observed that: (i) Nisei diabetic men in Seattle tended to be more overweight than Tokyo diabetic men, but not as overweight as Caucasian diabetic men; (ii) Nisei and Tokyo diabetic men consumed similar amounts of food, but less than Caucasian diabetic men; (iii) Nisei diabetic men consumed more total fat and less carbohydrates than Tokyo diabetic men; and (iv) Nisei diabetic men consumed proportionately as much fat (% of total calories as fat) as Caucasian diabetic men[14,15].

These early findings led to several conclusions and questions. For example, among those with diabetes, Japanese Americans were more overweight than native Japanese, but not as overweight as Caucasians, but Japanese Americans had higher diabetes rates than Caucasians. So was there anything else besides body size that was important? Also, we found that Japanese Americans had a dietary lifestyle that was more similar in

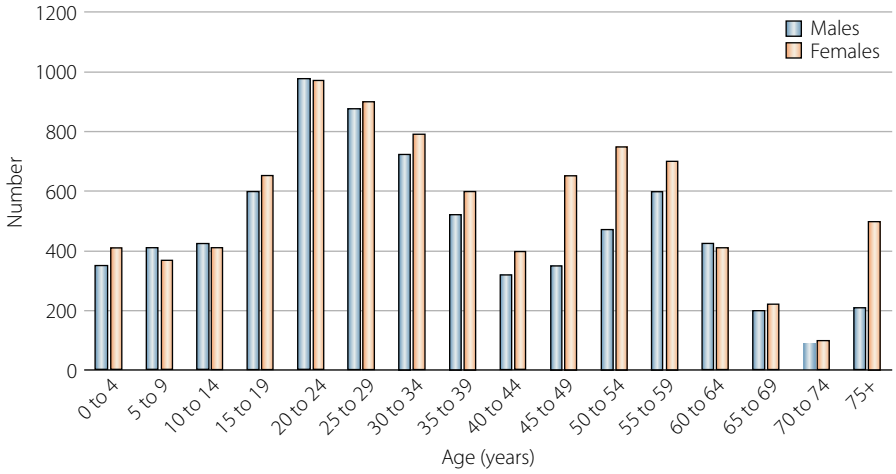

Figure 2 | The age distribution of Japanese Americans in Seattle in 1980 showing peaks at ≥75, 55 and 25 years, representing the Issei (immigrant first), Nisei (second) and Sansei (third) generations, respectively.

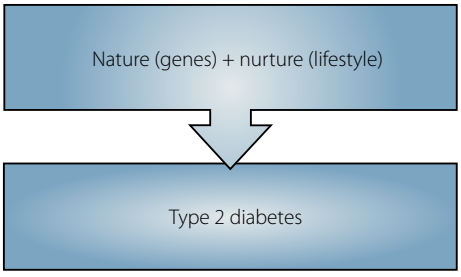

Figure 3 | Hypothesis underlying the Japanese American Community Diabetes Study.

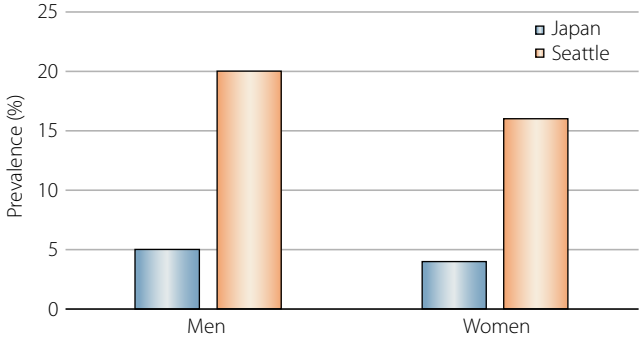

Figure 4 | Prevalence of type 2 diabetes in Japanese men and women aged ≥40 years in Tokyo and Seattle. Diabetes diagnosis by treatment for diabetes or using the former glucose criteria for diabetes from a 75-g oral glucose tolerance test: fasting glucose ≥140 mg/dL or 2-h glucose ≥200 mg/dL.

certain ways to that of Caucasians than of native Japanese. How was different lifestyle related to the development of diabetes in Japanese Americans?

BIRTH OF THE JAPANESE AMERICAN COMMUNITY DIABETES STUDY

We now had enough reason to proceed beyond the pilot study. The result of this was the Japanese American Community Diabetes Study (JACDS), an epidemiological study supported by funding from the National Institutes of Health that focused on the etiology and pathophysiology of type 2 diabetes[16–18]. The hypothesis underlying the JACDS was that an interaction between nature; that is, an inherent propensity towards the development of type 2 diabetes in Japanese, and nurture; that is, an adverse lifestyle environment, caused pathophysiological changes that resulted in hyperglycemia and type 2 diabetes (Figure 3). In order to examine this hypothesis, we studied men and women who were of pure Japanese ethnicity, either Nisei or Sansei, who resided in King County, Washington, in which the Seattle metropolitan area was the biggest population center. Early findings from this research showed that the prevalence of diabetes was indeed higher in Seattle, approximately fourfold higher in Seattle Nisei men and women than had been previously reported for Tokyo men and women of similar age (Figure 4)[19].

In addition, in a comparison of diabetic Nisei men and diabetic Japanese men in Tokyo, we observed that although mean glucose levels were very similar during a 3-h 75-g oral glucose tolerance test (OGTT) between these two groups, the corresponding insulin levels were much higher in Seattle. The relationship between the summed insulin and summed glucose plasma levels are shown in Figure 5; these showed that the Seattle men were very insulin resistant when compared with the native Japanese men[20]. The mean ages were similar for both groups, but the Seattle Nisei men had a greater mean body mass index (BMI), although still not as high as commonly seen in other ethnic/racial populations of diabetic patients in the USA. We concluded that Japanese Americans were more resistant to insulin action than native Japanese, and

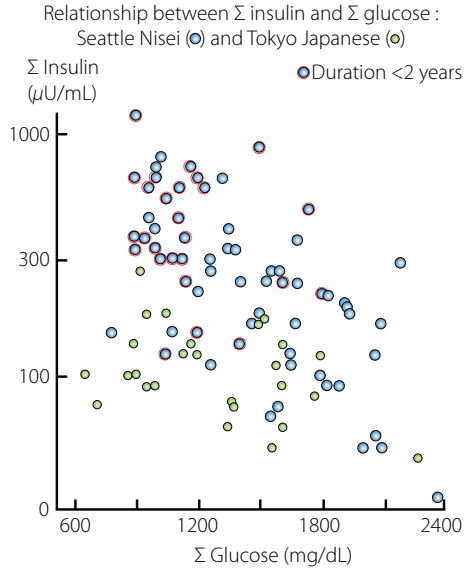

Figure 5 | Relationship between summed insulin and summed glucose during a 3-h 75-g oral glucose tolerance test in Seattle Nisei (●) and Tokyo Japanese (○) men.

that this might be because of their higher BMI. Thus, the higher prevalence of diabetes in Japanese Americans than in native Japanese could be because of the presence of more insulin resistance in Japanese Americans. However, there was still an important question that remained from my earlier discussion with Professor Kosaka: could it be that this reduction in insulin sensitivity has been superimposed on an inherently lower β-cell reserve in Japanese? If this were the case, then the higher prevalence of diabetes in Japanese Americans might be attributable to a greater number of individuals with insulin resistance that would in turn make those with lesser degrees of β-cell dysfunction more vulnerable to the development of hyperglycemia.

Another nagging question regarded BMI. 'Fatness' is important, but was there something else, for example body shape, that contributed (Figure 6)? The importance of body shape was reported by Jean Vague in a seminal paper published in 1956

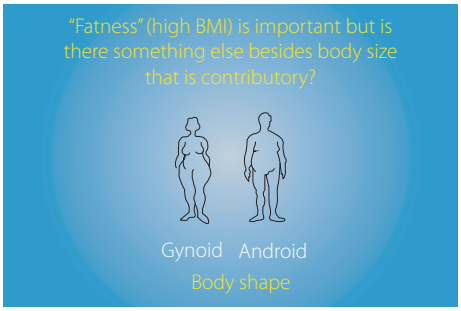

Figure 6 | Body shape patterns: gynoid and android. BMI, body mass index.

in which he described the android body habitus as predisposing to several conditions including diabetes[21]. Body shape, the extremes of which have been called android and gynoid, had been traditionally assessed by anthropometric means, such as skinfold thicknesses and body circumferences. The novel addition to our research was the use of CT to assess subcutaneous and intra-abdominal or visceral fat in all participants[22–26]. These CT scans were obtained by single slices in the chest, abdomen and thigh. Shown in Figure 7 are two computed tomography scans through the abdomen at the level of the umbilicus from two Nisei men, one of whom has diabetes (Figure 7a) and another who does not (Figure 7b). Tissue with the radiographic density of fat has been painted white in these scans. Clearly, the diabetic individual has much more intra-abdominal fat. Thus, very early on we became aware that those Nisei men with diabetes tended to have a larger intra-abdominal fat area at the level of the umbilicus as shown by this frequency distribution of intra-abdominal fat areas in normal and diabetic Nisei men (Figure 8). Subsequently, we found the same to be true for Nisei women as well as for Sansei men and women.

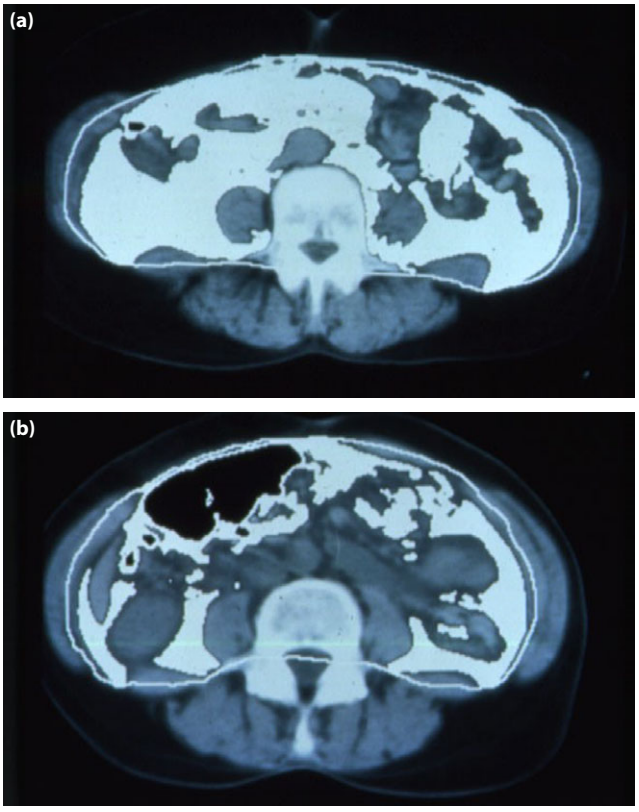

Figure 7 | Two computed tomography scans at the level of the umbilicus, (a) one of a Nisei man with diabetes and (b) the other of a Nisei man without diabetes. Tissue with the radiographic density of fat is shown in white.

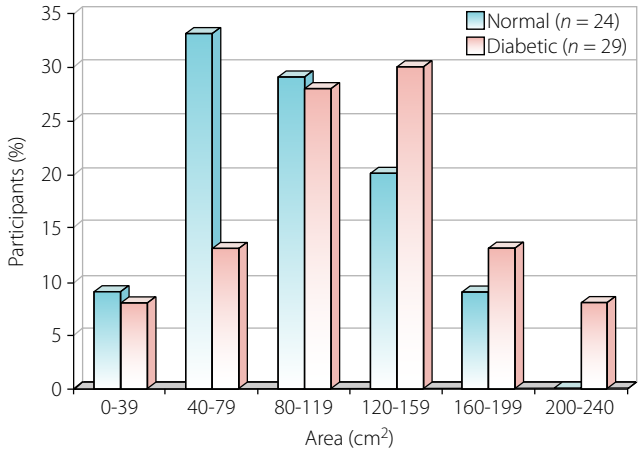

Figure 8 | Frequency distribution of intra-abdominal fat area at the umbilicus in normal and diabetic Japanese American men.

In 1989, based on what we were finding, we wrote in a review paper: 'The Japanese are a population with an inherent risk for developing diabetes. Among Japanese Americans in the United States, changes brought about through westernization in environmental variables such as nutrition, health habits, acting in conjunction with aging, weight gain, and central (visceral) adiposity, have furthered the development of insulin resistance, manifested as hyperinsulinemia, and glucose intolerance, either impaired glucose tolerance or diabetes'[27].

VISCERAL ADIPOSITY: AN INDEPENDENT RISK FACTOR FOR OBESITY-RELATED CONDITIONS

We have now reported visceral adiposity to be a powerful independent risk factor for several obesity-related conditions in Japanese Americans: coronary heart disease, impaired glucose tolerance, type 2 diabetes, hypertension, metabolic syndrome and insulin resistance[28–33]. The relationship of visceral adiposity to the development of insulin resistance is especially important, linking how insulin resistance might develop despite BMI levels that were not very high and thereby predispose Japanese Americans to diabetes.

In a prospective cohort analysis of future insulin resistance, we studied 407 Japanese American men and women not taking either oral hypoglycemic medications or insulin at baseline and at follow up[33]. Among the metabolic assessments were: (i) insulin resistance (homeostasis model assessment for insulin resistance [HOMA-IR] and fasting plasma insulin level); (ii) glycemia (fasting plasma glucose and 2-h plasma glucose); and (iii) β-cell function (incremental insulin response over glucose between fasting and 30-min of the OGTT). Measurements of adiposity were BMI, waist circumference and fat distribution by CT: (i) intra-abdominal fat area at the level of the umbilicus; (ii) subcutaneous fat area at the chest, at the abdomen and at the right thigh; (iii) total subcutaneous fat area calculated as the sum of the chest, abdomen and two times the right thigh subcutaneous fat areas; and (iv) total fat area calculated as the sum of the total subcutaneous and intra-abdominal fat areas.

Multiple linear regression analysis was used to model future insulin resistance as a function of other variables while adjusting for the baseline value of the same insulin resistance measure. For example, in model 1 intra-abdominal fat area at baseline was significantly associated with increased future HOMA-IR after adjusting for abdominal subcutaneous fat, HOMA-IR, incremental insulin response, 2-h glucose, age and sex at baseline (Table 2). The results were similar when fasting insulin was substituted for HOMA-IR. In additional models – models 2, 3, 4 and 5 – another adiposity measurement was substituted for abdominal subcutaneous fat: model 2, total subcutaneous fat area; model 3, total fat area; model 4, BMI; and model 5, waist circumference. In all of these, the results were similar to that seen with Model 1; that is, only intra-abdominal fat was associated with increased future insulin resistance.

Hence visceral adiposity, measured as intra-abdominal fat area, was associated with higher future insulin resistance, measured as either HOMA-IR or fasting plasma insulin, at follow up. This relationship was independent of baseline HOMA-IR or fasting plasma insulin, other measurements of adiposity, age, sex, 2-h plasma glucose level and incremental insulin response. Importantly, no other measurement of baseline regional or total adiposity was significantly correlated with future HOMA-IR or fasting plasma insulin in models that contained intra-abdominal fat. This provides a possible pathway for the link between adiposity and development of insulin resistance among Japanese Americans who are not as heavy as other racial populations in the USA.

DIET AND EXERCISE FOR ELIMINATING NIKKEI DIABETES STUDY

Diet and Exercise for Eliminating Nikkei Diabetes was a lifestyle modification randomized clinical trial developed as a proof-of-concept study[34,35]. The hypothesis was that aerobic

Table 2 | Multiple linear regression analysis of homeostasis model assessment of insulin resistance at follow up

Independent variables at baseline	Log_e (HOMA-IR)	
	β	*P*
Intra-abdominal fat area	0.0631	<0.001
Abdominal subcutaneous fat area	–0.0003	0.554
HOMA-IR	0.1327	<0.001
Incremental insulin response	0.0003	0.665
2-h plasma glucose	0.0002	0.791
Age	–0.0033	0.151
Female	–0.0692	0.227
Model R^2	0.362	

Findings were similar when fasting insulin was substituted for homeostasis model assessment of insulin resistance (HOMA-IR).

training and reduction of dietary animal fat in Japanese Americans with impaired glucose tolerance would ameliorate risk factors associated with progression to type 2 diabetes. Both men and women who had impaired glucose tolerance on two 75-g OGTT were randomly assigned to either of two groups and followed for 24 months: (i) a treatment group that received instruction in an isocaloric American Heart Association Step 2 diet (30% of calories as fat, 7% as animal fat and 55% as carbohydrate) and aerobic exercise training to 70% of heart rate reserve; and (ii) a control group that received instruction in an isocaloric American Heart Association Step 1 diet (30% of calories as fat, 10% as animal fat and 50% as carbohydrate) and stretching exercise. A total of 29 participants completed the treatment arm and 30 completed the control arm. OGTTs were carried out at 0, 6, 12 and 24 months, and at 0, 6 and 24 months we carried out an intravenous glucose tolerance test (to calculate insulin sensitivity as S_I and β-cell function as Air_g), anthropometric measurements, CT (body fat distribution), underwater weighing (percent body fat) and treadmill test (VO_{2max}).

The treatment group showed significantly lower bodyweight, percent body fat and intra-abdominal fat at 6 months, and for all of these plus waist circumference at 24 months when compared with the control group (Figure 9). In addition, the treatment group showed significantly greater insulin sensitivity (S_I) at 6 and 24 months, but β-cell function (Air_g) did not differ between the two groups (Figure 10). OGTTs were carried out at 6, 12 and 24 months, and 67% of the treatment group showed normal glucose tolerance at least once, significantly more often than the control group (30%). However, at 24 months the prevalence of normal glucose tolerance, although higher in the treatment group (40%), was not significantly different from the control group (30%).

We concluded from this proof-of-concept study that lifestyle modification consisting of dietary saturated fat restriction and prescription of aerobic exercise might be an effective approach to preventing type 2 diabetes in Japanese Americans by changing body composition and reducing insulin resistance.

INSULIN RESISTANCE VERSUS β-CELL DYSFUNCTION

Simply stated, when insulin resistance is great enough to offset the β-cells' ability to compensate, glucose levels increase (Figure 11). This is the issue that I had discussed with Professor Kosaka when we covered some of the difference between Japan and the USA regarding diabetes rates and risk factors. We were able to examine this in greater detail in a subanalysis of data from the Genetics of Non-Insulin Dependent Diabetes Study[36].

From the Genetics of Non-Insulin Dependent Diabetes cohort, we identified 531 individuals who had no prior history of diabetes, but on doing an OGTT, just 240 had normal glucose tolerance whereas the remainder had prediabetes (n = 191, impaired fasting glucose and/or impaired glucose tolerance) or diabetes (n = 100). The self-described ethnic/racial composition of these individuals was Caucasian (n = 217), Hispanic (n = 193), Asian (n = 66) or black (n = 55). Many of the Asians were from the JACDS. Both β-cell function, assessed as 30-min incremental insulin over 30-min incremental glucose derived from the OGTT, and insulin resistance, assessed as

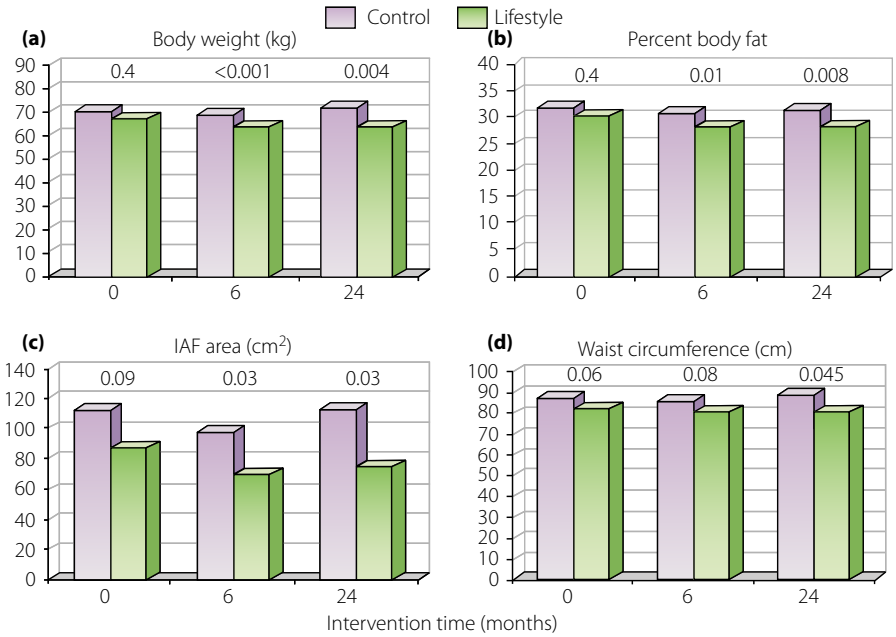

Figure 9 | Effect of lifestyle intervention on adiposity measurements at baseline and at 6 and 24 months in the Diet and Exercise for Eliminating Nikkei Diabetes study: (a) bodyweight, (b) percent body fat, (c) intra-abdominal fat area (IAF) and (d) waist circumference.

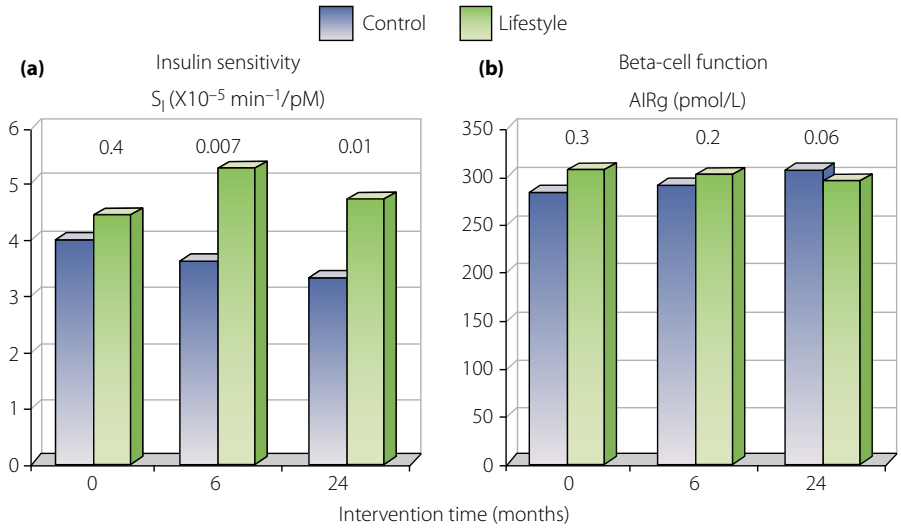

Figure 10 | Effect of lifestyle intervention on (a) insulin sensitivity and (b) β-cell function at baseline, and at 6 and 24 months in the Diet and Exercise for Eliminating Nikkei Diabetes study.

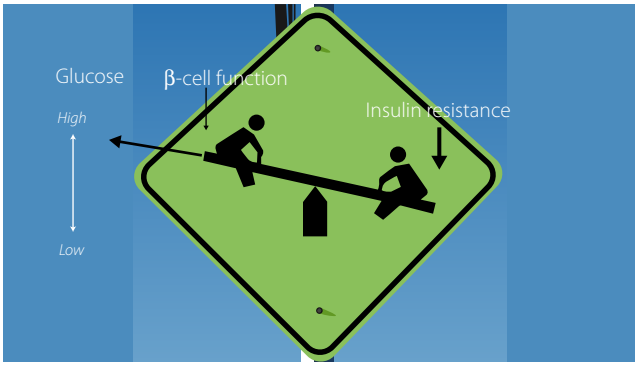

Figure 11 | Blood glucose levels are the result of the balance between β-cell function and insulin resistance.

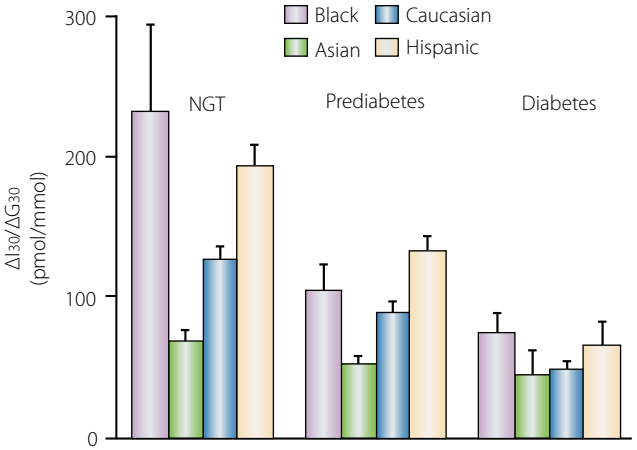

Figure 12 | β-Cell function in four ethnic/racial groups (black, Asian, Caucasian, Hispanic) according to glucose metabolism status: normal glucose tolerance (NGT), prediabetes and diabetes.

HOMA-IR, were examined by glucose metabolic status (normal, prediabetes, diabetes) for each racial/ethnic group. Caucasians were the reference group. As glucose tolerance deteriorated from normal to prediabetes to diabetes, β-cell function fell in all ethnic/racial groups (Figure 12). Asians had the lowest β-cell function, significantly so in the normal glucose tolerance and prediabetes categories. In the diabetic category, however, all of the groups were similarly impaired. As glucose tolerance deteriorated, insulin resistance increased in all groups (Figure 13). Asians had the lowest insulin resistance, significantly so in the normal and prediabetes categories. In the diabetic category, Asians had the same degree of insulin resistance as Caucasians. These findings suggested that increasing insulin resistance was unmasking the 'weak' β-cells that had been proposed by Professor Kosaka to be present in Japanese.

Thus, although many Asians are not obese by standards established in mainly white populations, if standards more appropriate to Asian populations are used, it is clear that body fat and especially the central (visceral) distribution of body fat are very important risk factors for type 2 diabetes in Asians. Similarly, insulin resistance contributes importantly to the development of type 2 diabetes in Asians, and may play an important role in unmasking an underlying less robust β-cell reserve in Asians.

BODYWEIGHT AND DIABETES RISK IN ASIANS

In the JACDS, we recognized early on that the definition of 'obesity' was likely to be different in Japanese Americans than in other populations: '…some ethnic groups are prone to gain weight with urbanization and westernization, and weight gain

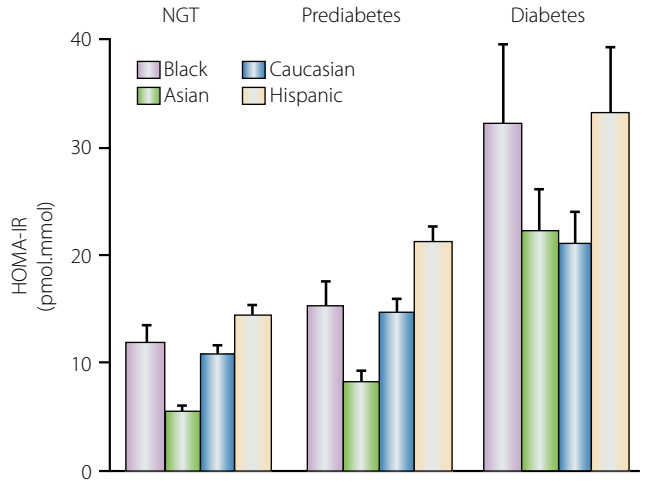

Figure 13 | Homeostasis model assessment of insulin resistance (HOMA-IR) in four ethnic/racial groups (black, Asian, Caucasian, Hispanic) according to glucose metabolism status: normal (NGT), prediabetes and diabetes.

is a powerful risk factor for diseases such as NIDDM, CHD, and hypertension. Asians constitute an ethnic group that seems to be especially at risk. The weight gain, however, need not lead to obesity as defined in predominantly Caucasian populations'[37].

The discrepancy between obesity rates and diabetes rates in Asians was illustrated very nicely in a paper appearing in Nature Medicine in 2004[38]. Shown in a figure from that paper was the prevalence of overweight and obesity in the USA, India, China, Japan and Singapore, and in a second graph, the prevalence of diabetes in these same countries. The definition of overweight was BMI 25 to <30 and for obesity, BMI ≥30 kg/m^2. Although the prevalence of overweight and obesity in all of the Asian nations was much lower than in the USA, the prevalence of diabetes in these nations was higher (Singapore) or nearly the same (Japan and India) as in the USA. For Japan, as an example, the prevalence of diabetes was nearly as high as in the USA, but the prevalence of overweight and obesity in Japan were a fraction of what it was in the USA (overweight approximately one-third and obesity approximately one-eighth). Professor Yutaka Seino is quoted in that article: 'If the Japanese had the same BMI distribution as the US, 80% of the population would have diabetes.' The message to be learned from these data is that Asians are at risk for diabetes at bodyweight levels much lower than in non-Asians.

Very recently, we carried out a careful review of published data collected in Asian Americans, looking at the relationship between BMI and risk for diabetes. In previous versions of their annual 'Standards of Medical Care in Diabetes,' the American Diabetes Association has recommended that testing for diabetes or prediabetes in asymptomatic adults should be considered in all who are overweight (BMI ≥25 kg/m^2). Based on our review, we published a position statement and a research paper in which we recommended that screening for diabetes in Asian Americans should be carried out at BMI ≥23 kg/m^2[39,40]. This recommendation was incorporated into the 2015 'Standards of Medical Care in Diabetes'[41].

CANARY IN THE COAL MINE

In 1992, as we were beginning to understand what was happening in Japanese Americans, I wrote the following in a review: 'Because of the rapidity with which western influences can now be introduced, the prevalence of NIDDM in many non-migrant, native Asian populations may be expected to increase and reach those levels already seen in migrant Asians unless measures are taken to reduce this risk. This is a significant public health issue because the large populations in many Asian countries will assure that if this prediction is correct, NIDDM will become a major health problem in Asia in the near future'[42]. In other words, what we were finding in Japanese Americans was a harbinger or warning of future deterioration of health, such as developing type 2 diabetes, among native Japanese and other persons of Asian origin. Unfortunately, this is being found to be correct. For example, the global estimates of the prevalence of diabetes for 2011 and 2030 published by Whiting *et al.* in 2011[43] showed that there were 205 million cases of diabetes in 2011 in those countries that fall within Asia, approximately 56% of all cases worldwide, while in 2030, the projection was 319 million cases in Asia, or 58% of all cases worldwide. Japanese Americans have been figurative 'canaries in the coal mine.'

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culture studies; (iv) Dr Tomoshige Hayashi joined the group in 2001 from Japan to work with Dr Boyko for 3 years, and has been instrumental in continuing a very productive analysis of data from this research even after returning to Japan; and (v) Dr Marguerite McNeely was an epidemiologist who joined our research group relatively late in 1997 when we were looking for additional epidemiological expertise and who promptly took up much of the analysis of our data, but a promising career ended prematurely when she succumbed to an aggressive brain tumor in 2014. I also gratefully acknowledge the support and assistance provided by Dr Kinori Kosaka, Dr Yasuo Akanuma and Dr Yasunori Kanazawa at the University of Tokyo, and Dr Nobusada Kuzuya at the Asahi Institute in Tokyo during the pilot study and the early years of the JACDS, and the many skilled staff members at the University of Washington, especially Pamela Asberry, Jane Shofer, Christine Tsunehara, Pamela Yang and the staff of the General Clinical Research Center. I am particularly grateful for the unswerving support and cooperation of the King County Japanese American community and our Community Advisory Board, without which it would not have been possible to carry out the research.

DISCLOSURE

The author declares no conflict of interest.

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