High Frequency of Pre-Diabetes, Undiagnosed Diabetes and Metabolic Syndrome among Overweight Arabs in Israel

Muhammad A. Abdul-Ghani MD PhD[1], Muhammad Sabbah MD[1], Basel Muati MD, Nachle Dakwar MD[1], Hesham Kashkosh BNS, Oscar Minuchin MD[1], Pnina Vardi MD[1,2] and Itamar Raz MD[3]
for the Israeli Diabetes Research Group (IDRG)

[1]Department of Diabetes, Lin Medical Center, Haifa, Israel
[2]Section of Internal Medicine, Felsenstein Medical Research Center (Beilinson Campus), Petah Tiqva, Israel
Affiliated with Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[3]Diabetes Unit, Haddasah University Hospital, Jerusalem, Israel

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Abstract

Background: Increased insulin resistance, which is associated with obesity, is believed to underlie the development of metabolic syndrome. It is also known to increase the risk for the development of glucose intolerance and type 2 diabetes. Both conditions are recognized as causing a high rate of cardiovascular morbidity and mortality.

Objectives: To assess the prevalence of metabolic syndrome and different glucose intolerance states in healthy, overweight Arab individuals attending a primary healthcare clinic in Israel.

Methods: We randomly recruited 95 subjects attending a primary healthcare clinic who were healthy, overweight (body mass index > 27) and above the age of 40. Medical and family history was obtained and anthropometric parameters were measured. Blood chemistry and oral glucose tolerance test were performed after overnight fasting.

Results: Twenty-seven percent of the subjects tested had undiagnosed type 2 diabetes according to WHO criteria, 42% had impaired fasting glucose and/or impaired glucose tolerance and only 31% had a normal OGTT. Metabolic syndrome was found in 48% according to criteria of the U.S. National Cholesterol Education Program, with direct correlation of this condition with BMI and insulin resistance calculated by homeostasis model assessment. Subjects with metabolic syndrome had a higher risk for abnormality in glucose metabolism, and the more metabolic syndrome components the subject had the higher was the risk for abnormal glucose metabolism. Metabolic syndrome predicted the result of OGTT with 0.67 sensitivity and 0.78 specificity. When combined with IFG, sensitivity was 0.83 and specificity 0.86 for predicting the OGTT result.

Conclusions: According to our initial evaluation approximately 70% of the overweight Arab population in Israel has either metabolic syndrome or abnormal glucose metabolism, indicating that they are at high risk to develop type 2 diabetes and cardiovascular morbidity and mortality. This population is likely to benefit from an intervention program.

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OGTT = oral glucose tolerance test
BMI = body mass index
IFG = impaired fasting glucose

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The metabolic syndrome is characterized by the clustering of several cardiovascular risk factors including central obesity, hypertension and dyslipidemia. Reduction in tissue sensitivity to insulin action, known as insulin resistance, is widely accepted as the underlying mechanism that leads to development of the syndrome [1]. High insulin resistance is also associated with high risk for development of type 2 diabetes [2]. Epidemiologic studies have demonstrated that subjects with metabolic syndrome or type 2 diabetes have high cardiovascular morbidity and mortality rates [3]. Furthermore, diabetic subjects with metabolic syndrome were shown to have a worse cardiovascular prognosis than type 2 diabetic subjects without the syndrome [4].

Insulin resistance, type 2 diabetes and metabolic syndrome are frequently associated with obesity and overweight. The recent worldwide dramatic increase in the prevalence of type 2 diabetes and metabolic syndrome is attributed to the epidemic of obesity that occurred in the last decade [5]. Improving insulin resistance after reduction in body weight, and increasing physical activity have been shown to significantly reduce the incidence of type 2 diabetes in high risk populations [6,7].

Obesity and type 2 diabetes are commonly found in Arab populations [8–10] and recent studies have demonstrated an increasing prevalence of metabolic syndrome in various Arab communities [11–13]. In this study we assessed the prevalence of metabolic syndrome and the pre-diabetes state in an overweight and obese Arab population in Israel.

Subjects and Methods

Study population

The study included 95 overweight Arab subjects (52 females, 43 males) attending the primary healthcare clinic of Clalit Health Services in an Arab village in northern Israel. The clinic provides primary healthcare services to 10,652 people, who constitute 90% of

the total population. All subjects in the study were over 40 years old with a body mass index above 27 and participated in a screening program to identify individuals at high risk for development and prevention of type 2 diabetes. In this program, all subjects above 40 years old with BMI >27 attending the primary care clinic, independent of the reason for their visit, were offered an oral glucose tolerance test to assess their risk for future development of diabetes. Of the first 109 subjects offered an OGTT, 100 responded positively and we report their results. Five subjects had incomplete data and were therefore excluded from the analysis. All subjects were healthy and had no known abnormality in glucose homeostasis. None of them was taking medication known to affect glucose metabolism.

Methods

All subjects provided a detailed medical and family history and underwent a complete physical examination. Subjects' body weight was measured, in light clothes without shoes, with a digital scale to the nearest 0.1 kg. Height was measured with a wall-mounted stadiometer. Body mass index was calculated. Waist circumference was measured by a metric tape at the largest abdominal circumference. Blood pressure was measured twice with a sphygmomanometer after at least 10 minutes rest with 30 minutes between the two measurements, and the average of the two measurements was used for the study.

Complete laboratory evaluation was performed during fasting, including blood biochemistry, hematology, and lipid profile. Fasting blood glucose, insulin and hemoglobin A1C were also measured. An oral glucose tolerance test was performed, and blood samples for glucose and insulin were drawn after overnight fasting at 0, 30, 90 and 120 minutes following ingestion of 75 g glucose. The results were used to determine tolerance to carbohydrates as well as beta cell function and insulin sensitivity.

Definition of glucose categories and metabolic syndrome

Glucose intolerance state was defined according to the 1985 World Health Organization [14] and 1997 American Diabetes Association criteria [15]. The recent low cutoff point of fasting blood glucose (100–126 mg/dl) was used to define subjects with impaired fasting glucose [16]. Metabolic syndrome was defined according to criteria of the National Cholesterol Education Program [17]. Subjects were defined as having the metabolic syndrome if they met three or more of the following criteria: a) waist circumference >88 cm in women and >102 cm in men, b) high density lipoprotein <50 mg/dl in women and <40 in men, c) triglycerides >150 mg/dl, d) blood pressure >130/85 mmHg, and e) fasting glucose >100 mg/dl. Insulin resistance was calculated by the homeostasis model assessment using the fasting level of plasma glucose and insulin [18].

Statistical analysis

Data analysis was performed with Excel software. Data are presented as means ± standard deviation. Statistical significance was tested with Student's *t*-test for unrelated samples, and significance was determined at $P < 0.05$.

Table 1. Anthropometric and metabolic parameters of the whole study group and stratification according to the presence of metabolic syndrome

	Whole study group (1)	With metabolic syndrome (2)	Without metabolic syndrome (3)	*P* value (2 vs. 3)
N.	95	45	50	
Age (yrs)	49.5 ± 10.9	51.3 ± 9.8	47.97 ± 11.8	0.16
BMI	32.68 ± 6.2	34.13 ± 7.2	31.2 ± 5.2	0.038
Waist (cm)	109.1 ± 14.5	113.8 ± 16.9	105.9 ± 12.9	0.0138
Females (%)	56.8	44.4	56.0	0.32
Hypertension (%)	24.7	39.5	16.7	0.0088
High density lipoprotein (mg/dl)	42.2 ± 9.5	39.5 ± 5.4	45.2 ± 11.5	<0.0001
Low density lipoprotein (mg/dl)	110.0 ± 30.2	107.6 ± 32.4	111.7 ± 29.8	0.302
Triglycerides (mg/dl)	189.5 ± 125.5	230.7 ± 52.2	158.4 ± 32	0.039
Cholesterol (mg/dl)	193.7 ± 38.9	194.2 ± 37	192.7 ± 32	0.19
Fasting blood glucose (mg/dl)	106.2 ± 16.7	113.4 ± 16.9	97.9 ± 13.5	0.0409
Fasting insulin (pmol/ml)	97.1 ± 67.3	113.2 ± 45.9	84.1 ± 62	0.037
Insulin resistance	4.22 ± 3.37	4.96 ± 3.75	3.155 ± 2.48	0.0056

Table 2. Prevalence (%) of different glucose intolerance groups according to OGTT result

	2 hr blood glucose value (mg/dl)			Fasting blood glucose (mg/dl)
	>200	200–140	<140	
43.2%	1.1	10.5	31.6	>100
39.9%	8.4	18.9	12.6	100–125
16.9%	6.3	7.4	3.2	<126
100%	15.8	36.8	47.4	Total

Results

The mean age of the 95 study subjects (52 females, 43 males) was 49.5 ± 10.9 years and the mean BMI was 32.68 ± 6.2. Table 1 presents the anthropometric and metabolic characteristics of the study population.

Table 2 depicts the glucose tolerance status of the study population as assessed by OGTT. Only 31% of subjects had a normal OGTT, 27% had undiagnosed diabetes according to WHO criteria, 37% had impaired glucose tolerance, and 40% had IFG according to the new IFG cutoff point. Thirteen percent had IFG only while their 2 hour glucose was normal, whereas 11% of the subjects had IGT only with normal fasting glucose. Nineteen percent of the subjects had both IGT and IFG and were defined as having combined glucose intolerance.

According to NCEP criteria, 48% of the subjects had metabolic syndrome. The most frequent component of metabolic syndrome was central obesity and high triglyceride levels, which were observed in 65% and 66% of the subjects respectively. Low HDL-cholesterol was observed among 56% of the population, and high

IGT = impaired glucose tolerance
NCEP = National Cholesterol Education Program
HDL = high density lipoprotein

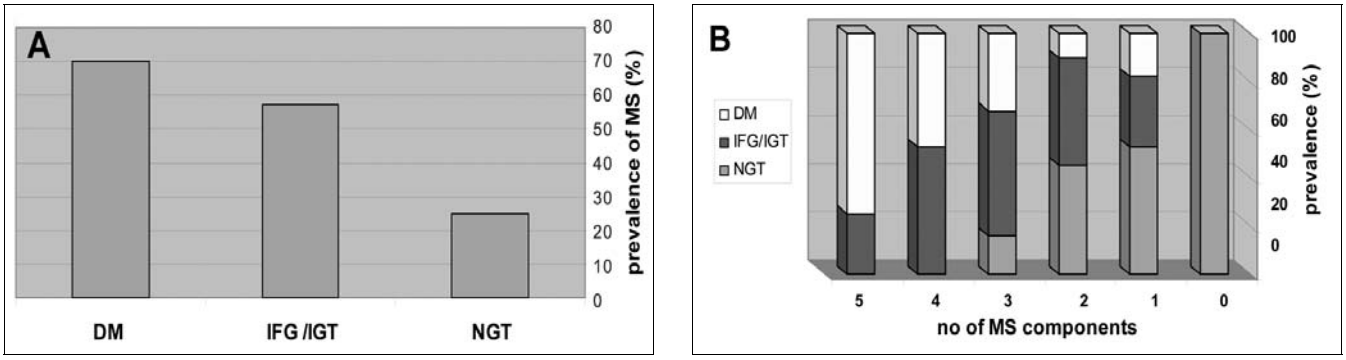

Figure 1. Relation between metabolic syndrome and glucose intolerance state. **[A]** Prevalence of the syndrome among subjects with different states of glucose intolerance. **[B]** Distribution of the different glucose intolerance categories according to the number of syndrome components. DM = diabetes mellitus, IFG = impaired fasting glucose, IGT = impaired glucose tolerance, NGT = normal glucose tolerance, MS = metabolic syndrome.

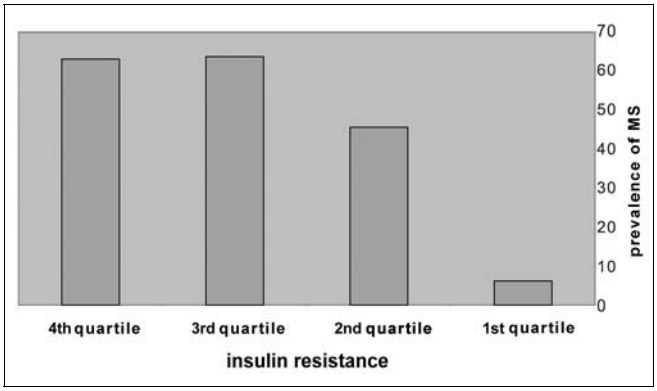

Figure 2. Prevalence of metabolic syndrome according to insulin resistance. Insulin resistance was calculated by HOMA, and all subjects were grouped according to the level of their insulin resistance; the first quartile had the lowest value and the fourth had the highest.

blood pressure among 25%. Only 4% of the study group had all five components of the metabolic syndrome. Subjects with metabolic syndrome had significantly higher levels of triglycerides (280 vs. 200 mg/dl), waist circumference (99 vs. 96 cm), fasting glucose (122 vs. 119 mg/dl) insulin (189 vs.150 pmol/ml), and lower HDL-cholesterol (34 vs. 43 mg/dl) than subjects without metabolic syndrome [Table 1].

A direct correlation was found between the metabolic syndrome and BMI (r = 0.3561, P = 0.0033). This correlation remained statistically significant after adjustment for age, gender and insulin resistance (P = 0.032). The metabolic syndrome correlated also with insulin resistance calculated by HOMA (r = 0.264, P = 0.0189) [Figure 1], and the correlation remained significant after adjustment for age, gender, and BMI (P = 0.0067). However, it was only weakly correlated with age (r = 0.1244) and this correlation was not statistically significant (P = 0.312). In addition, the metabolic syndrome was significantly correlated with both fasting and 2 hour glucose status of glucose intolerance. Its correlation with fasting glucose was stronger than with 2 hour glucose (r = 0.47, P = < 0.0001 and r = 0.291, P = 0.0089 respectively), and this correlation remained significant after adjustment for age, gender, BMI and insulin resistance. When subjects were grouped according to their glucose intolerance status, subjects with normal glucose tolerance had the lowest prevalence of metabolic syndrome (25%), subjects with type 2 diabetes had the highest prevalence (70%), while intermediate prevalence was found in subjects with IFG or IGT of 59% [Figure 1A].

Figure 1B shows the distribution of different glucose metabolism categories according to the number of metabolic syndrome components. All subjects who had four to five metabolic syndrome components had some form of abnormal glucose metabolism. As the number of components increased, so the frequency of subjects with diabetes or IFG and/or IGT increased, with a decline in the frequency of subjects with normal glucose metabolism [Figure 1B].

When the presence of metabolic syndrome was used to predict OGTT result, it had a sensitivity of 0.76 and specificity of 0.41 in predicting subjects with undiagnosed diabetes. When the metabolic syndrome was used to predict subjects with undiagnosed diabetes or IGT, its sensitivity declined to 0.67 but its specificity increased to 0.78. When compared to the prediction ability of IFG, IFG had a significantly higher sensitivity than metabolic syndrome in predicting subjects with undiagnosed diabetes (0.96 and 0.76 respectively, P = 0.04) but similar specificity (0.44 and 0.41 respectively, P = 0.48). In predicting subjects with either undiagnosed diabetes or IGT, both IFG and metabolic syndrome were similar, with sensitivity of 0.78 and 0.67 (P = 0.19) and specificity of 0.78 and 0.72, respectively (P = 0.75). The combination of both IFG and metabolic syndrome does not add to the prediction ability of IFG in predicting subjects with undiagnosed diabetes. The sensitivity and specificity were not significantly different from those of IFG alone. However, in predicting IGT or subjects with undiagnosed diabetes, combining metabolic syndrome with IFG improves its sensitivity and specificity only slightly. The difference did not reach statistical significance (from 0.76 to 0.83, P = 0.55, and from 0.72 to 0.86, P = 0.086 respectively).

Discussion

This study demonstrates that among subjects in the clinic population studied, those above the age of 40 years who are

HOMA = homeostasis model assessment

overweight and/or obese (BMI > 27) are at very high risk to develop type 2 diabetes and cardiovascular disease. Only one-third of the subjects tested had normal OGTT, while 26% had undiagnosed type 2 diabetes. This group of diabetic patients can be considered a group at high risk for development of diabetic complications. Since it is well documented [19] that treatment of diabetes to targets (hemoglobin A1C < 7) significantly reduces diabetic complications, the identification and treatment of this large population may have a significantly favorable effect on their health and well-being.

The prevalence of undiagnosed diabetes in this cohort is higher than that observed in an earlier study performed among Israeli workers, and could be due to the difference in population selection [20]. While the present study included subjects above the age of 40 and with BMI >27, earlier studies evaluated subjects in the general population. Advanced age and BMI are two risk factors highly associated with diabetes development and may well contribute to the high prevalence of undiagnosed diabetes in our survey. Furthermore, in this study we used OGTT to diagnose type 2 diabetes, while the diagnosis in the earlier study was based on the level of fasting glucose, which is a less sensitive method than OGTT in detecting diabetes. OGTT was performed only for high risk subjects [20]. Ethnic differences – Arab origin in this study and Jewish origin in the other – may also have contributed to this difference. A very high prevalence of type 2 diabetes has been reported in several Arab populations: 18% of Arab Americans living in Detroit [9], and up to 32% of the whole population in Bahrain [8], compared to a lower prevalence of type 2 diabetes (7%) in Caucasians [21,22]. Although subjects in our cohort were selected randomly, certain factors may have caused bias in the results. The sample selected is not representative of all adult outpatient clinics; furthermore, it was selected from subjects who attended the primary care clinic frequently, thus it may differ from those rarely attending the clinic. Despite the possible bias in subject selection, the results of this study suggest that a significant portion of the Arab population in Israel may be at high risk for type 2 diabetes and cardiovascular morbidity. It also emphasizes the urgent need for a comprehensive survey to assess this risk in the entire Arab population in Israel in order to implement an effective intervention program.

Forty-two percent of the study population had evidence of impaired glucose metabolism, IFG and/or IGT, and therefore could be considered as being pre-diabetes. This prevalence rate of pre-diabetes is twice the rate reported in other populations. Pre-diabetic subjects are at very high risk for progression to type 2 diabetes, with an annual progression rate of 5–10% among various populations [23]. Applying this progression rate of type 2 diabetes to the 10,000 subjects attending our outpatient clinic, it can be expected that between 250 and 500 new cases of type 2 diabetes will develop in the next 5 years, compared to 320 subjects currently diagnosed with the disease. Such a dramatic increase in the prevalence of diabetes, with the burden that it poses on both public health and economic expenditure, should urge healthcare providers to initiate an intervention program in this population to arrest this epidemic-like incidence of the disease.

The prevalence of metabolic syndrome observed in this population is also very high. Almost half of the subjects tested in this study had metabolic syndrome, with a rate almost double that in the American population [24]. It is also higher than the rate reported in other Arab populations [11–13]. Our inclusion criteria (age >40 and BMI >27) may have also contributed to the high prevalence of metabolic syndrome. Due to the strong impact of lifestyle on the development of metabolic syndrome, the rapid transition from a rural to urban way of life that Arab populations in Israel underwent in recent decades may have contributed to the high rate of metabolic syndrome observed in this population.

The rate of metabolic syndrome in this study correlated directly with BMI and insulin resistance [Figure 2], which is consistent with the established central role for obesity and insulin resistance in the pathogenesis of the syndrome [1,2]. Due to the increased risk for cardiovascular morbidity and mortality in people with metabolic syndrome [3], we can assume that about half the subjects older than 40 years with BMI >27 in this population are at high risk for cardiovascular disease. Therefore, an intervention program aimed at reducing obesity and encouraging physical activity will also have a favorable effect on cardiovascular morbidity and mortality in this community.

Our results confirm epidemiologic studies demonstrating that subjects with metabolic syndrome are at high risk for type 2 diabetes [25]. Furthermore, the more components of metabolic syndrome the subject has, the higher the risk for abnormality in glucose metabolism [Figure 1B]. All subjects who had four or more components of the syndrome had an abnormality in glucose metabolism. When we used the diagnosis of metabolic syndrome to predict the result of OGTT, it had reasonable sensitivity and specificity. Although it was lower than the prediction ability of fasting glucose, it was only statistically significant for sensitivity in predicting diabetes. The interesting observation was that combining fasting glucose with metabolic syndrome for predicting OGTT results had the best sensitivity and specificity.

This study was performed in a relatively small number of subjects and these results need to be validated in a larger cohort. Despite this shortcoming it still demonstrates that normal individuals in this community who are at high risk for having undiagnosed abnormal glucose metabolism can be predicted, with high sensitivity and specificity, by simple clinical parameters (blood pressure, waist circumference) and laboratory tests (fasting glucose and blood lipids), which are widely available in a primary care setting.

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Correspondence: Dr. M.A. Abdul-Ghani, Diabetes Division, University of Texas Health Science Center, 7703 Floy Curl Drive, San Antonio, TX 78229, USA.
Phone: (1-210) 567-6691
Fax: (1-210) 567-6554
email: muhammadag@hotmail.com