

Glucose intolerance and risk for cardiovascular disease in obese individuals

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Recently, obesity is gaining importance as a major predisposing factor for diabetes and cardiovascular risk. The aim of this study was to assess the risk of diabetes and cardiovascular disease in obese individuals. Fasting blood glucose, glycosylated hemoglobin (GHb), fructosamine levels, total cholesterol to high-density lipoprotein cholesterol ratio and the response of free fatty acids (FFA) to glucose during oral glucose tolerance test (OGTT) were determined in 10 non-obese nondiabetic controls and in 19 obese nondiabetic subjects. Glycosylated hemoglobin was assessed by column chromatography, fructosamine and HDL-cholesterol by colorimetry and free fatty acids were measured by titrimetry. 1) GHb levels were $5.320 \pm 0.842\%$ in the non-obese control group and $5.639 \pm 0.663\%$ in obese group ($p > 0.05$). 2) Fructosamine levels in the non-obese control group and in the obese group were 2.656 ± 0.223 and 1.862 ± 0.283 mmol/L, respectively ($p < 0.01$). 3) During the OGTT, a reduction of 41% was observed in FFA concentrations in response to glucose in the non-obese controls and of 26% in the obese subjects. 4) Total cholesterol/high-density lipoprotein cholesterol ratio was 3.110 ± 0.731 in the non-obese controls and 4.167 ± 1.231 in the obese group ($p < 0.05$). The diminished FFA response to glucose suggests glucose intolerance in obese nondiabetic individuals. Furthermore, the elevated total cholesterol/HDL-cholesterol ratios support increased risk for atherosclerosis in these subjects. [Turk J Med Res 1995, 13(4):147-150]

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Obesity is a major nutritional problem mentioned as a predisposing factor for cardiovascular risk and diabetes. The effects of excess weight on death from diabetes mellitus are particularly striking. Both the duration and magnitude of obesity increase risk of diabetes (1). Obesity appears to aggravate the development of diabetes and weight loss appears to reduce the risk of this disease (2).

The obese individual demonstrates a number of endocrine and metabolic abnormalities related to pancreatic function. Among these, alterations in glucose tolerance and insulin concentrations are the most frequent. Hypertrophy of adipocytes results in a decrease in insulin receptor distributions on the cell surface leading to glucose intolerance (3). Studies on the metabolic origin of insulin resistance in obesity suggest that the prolonged duration of increased lipid oxidation in the obese may be the initial cause leading to Type 2 diabetes. Decreased glucose utilization

resulting from increased lipid oxidation is accused of inhibiting glycogen synthase activity together with inhibition of glucose storage and impaired glucose tolerance (4).

Fasting blood glucose, oral glucose tolerance test (OGTT), glycosylated hemoglobin and fructosamine assays are the conventional analyses for the assessment of glucose tolerance. However, in the early stages of glucose intolerance, these tests may not be sufficient for the diagnosis of impaired glucose tolerance. The reduced response of free fatty acids to glucose in the OGTT may reflect an impaired glucose tolerance in the early stage (5).

Obesity by itself may constitute a cardiovascular risk factor by impairing glucose tolerance. Recent studies emphasize the association between total body fatness, body fat distribution and several coronary heart disease risk factors (6,7) and examine the impact of weight loss (8). Body mass index (BMI) is the most widely used index of overweight based on body weight in relation to height. This index shows a good correlation with body fat, is unaffected by age, sex and bone structure and may be used to assess the magnitude of potential health risks associated with overweight (2). The aim of this study was to assess

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the risk of diabetes and cardiovascular disease in obese subjects. For this purpose, fasting blood glucose, oral glucose tolerance, glycosylated hemoglobin (GHb), fructosamine, free fatty acids (FFA), total cholesterol/HDL-cholesterol ratios and BMI were determined in obese and nonobese nondiabetic subjects.

MATERIALS AND METHODS

19 patients (18 women, 1 man) aged between 17-68 years (mean±SD: 44.63±13.23) submitted to the obesity clinic of the Endocrinology Department of Ege University Medical School constituted of 10 healthy nonobese (8 women, 2 men) subjects aged between 22-52 years (mean±SD:33.90±8.70) with no known history of disease.

Overnight fasting (12-14 hours) blood samples from peripheral veins were obtained from all subjects and the following determinations were performed:

1) Serum glucose was determined on the Hitachi 704 automated system by the glucose oxidase method.

2) Glycosylated hemoglobin values in hemolysate were determined by cation exchange column

chromatographic method with the Helena GHb Quick Column 5344 minicolumn kit.

3) Serum fructosamine concentrations were measured by a colorimetric method based on the reduction of nitroblue tetrazolium by 1-deoxymorpholinofructose (DMF) (9).

4) Plasma free fatty acids were assayed by the titrimetric method modified from Dole (10).

5) Serum total cholesterol and HDL-cholesterol were measured on the Hitachi 704 autoanalyzer by the cholesterol oxidase method and total cholesterol/HDL-cholesterol ratios were calculated.

Body mass index was used for the estimation of total body fatness and was calculated as:

$BMI=W/H^2$ where W=body weight in kilograms and H=height in meters

Age, height, weight and BMI values of all subjects are summarized in Table 1.

RESULTS

Results are summarized in Table 2.

1. Serum glucose:

a) Fasting serum glucose (FSG) levels were 81.30±12.74 mg/dL for the nonobese control group and 92.89±12.89 mg/dL for the obese group. The difference was not statistically significant ($p>0.05$).

b) Serum glucose levels in the first hour of the OGTT were 120.0±18.94 mg/dL for the nonobese control group and 115.89±15.25 mg/dL for the obese group. The difference between two groups was not significant ($p>0.05$).

2. Glycosylated hemoglobin (GHb):

The mean value was 5.320±0.842% for the non-obese and 5.639±0.663% for the obese group ($p>0.05$). No significant difference was obtained between the two groups.

3. Fructosamine:

The mean value was 2.656±0.223 mmol/L for the nonobese controls and 1.862±0.283 mmol/L for the obese subjects ($p<0.01$).

4. Free fatty acids (FFA):

a) FFA levels in the fasting state were not statistically different in the two groups: 1.333±0.374 mmol/L for the nonobese and 1.144±0.343 mmol/L for the obese subjects ($p<0.05$).

b) No significant difference was observed in the FFA values in the first hour of the OGTT between control and obese subject: 0.7740 During the OGTT 0.27749 and 0.7099±0.3743 mmol/L, respectively ($p>0.05$).

During the OGTT, a reduction of 41% was observed in the FFA levels in response to glucose in the non-obese group and of 26% in the obese group.

Table 1. Subject characteristics (mean±SD)

	Control	Obese
Age (years)	33.90±18.70	44.63±13.23
Height (meters)	1.66±4.95	1.585±0.065
Body weight (kg)	59.70±4.95	90.68±17.00
Body mass index (kg/m ²)	21.67±1.219	36.34±7.80

Table 2. Serum glucose, glycosylated hemoglobin, fructosamine, free fatty acids and total cholesterol/HDL-cholesterol ratio of obese and non-obese subjects

	Non-obese	Obese	P
Fasting serum glucose (mg/d.l)	81.30±12.74	92.89±12.89	>0.05
Serum glucose (OGTT1 st hour, mg/dl)	120.0±18.94	115.89±14.42	>0.05
GHb (%)	5.320±0.842	5.639±0.663	>0.05
Fructosamine (mmol/L)	2.656±0.223	*1.862±0.283	*<0.01
FFA (Fasting, mEq/L)	1.333±0.374	1.144±0.343	>0.05
FFA (OGTT 1 st hour)	0.7740±0.2749	0.7099±0.3743	>0.05
T.Chol./HDL-Chol. (%)	3.110±0.731	*4.167±1.231	*<0.05

Table 3. Fructosamine correlations

	Obese (n-19)		Nonobese (n-10)	
	r	P	r	P
GHb	0.456	<0.05	0.655	<0.05
Fasting blood glucose	0.472	<0.05	0.650	<0.05
BMI	-0.323	<0.05	0.437	>0.05

5. Total cholesterol/high density lipoprotein cholesterol ratio was 3.110 ± 0.731 in the nonobese and 4.167 ± 1.231 in the obese subjects. The difference was significant ($p < 0.05$).

There were significant correlations between: fructosamine and BMI ($r = 0.323$, $p < 0.05$) (Table 3), BMI and fasting FFA ($r = 0.607$, $p < 0.01$), BMI and T.Chol/HDL-Chol.ratio ($r = 0.546$, $p < 0.01$), fasting glucose and fasting FFA ($r = 0.356$, $p < 0.05$), first hour glucose and 1st hour FFA ($r = -0.197$, $p < 0.05$) in obese subjects.

DISCUSSION

Experimental and clinical studies have shown that hyperinsulinemia and ineffective glucose utilisation in tissues contribute to the impaired glucose tolerance in obese nondiabetics. In a recent experimental study performed on genetically obese Zucker rats, glucose intolerance and insulin resistance became more pronounced with aging, but basal insulinemia was unaffected (11). In other studies which demonstrated increased basal levels of insulin the enhanced secretion of this hormone promoted triglyceride synthesis in the adipose tissue, thus increasing fat deposition in the same tissue (2,12).

Impaired glucose tolerance accelerates atherosclerosis. Cardiovascular disease is more frequent among obese and diabetics. FFA, cholesterol and VLDL are increased in the obese subjects and the oxidative modification of lipoproteins is reported to have cytotoxic effects for the vascular endothelium (13). On the other hand, high total cholesterol/HDL-cholesterol ratios are considered as significant risk factors in atherosclerosis (14). Accordingly, the significant elevation of total cholesterol/HDL-cholesterol ratio that we found in our obese group supports the increased atherosclerosis risk in these subjects.

In our study, no significant difference was observed in fasting serum glucose and first hour OGTT glucose values in obese subjects when compared with controls. This suggests that glucose tolerance is not yet impaired in these obese subjects. On the other hand, the response of FFA to glucose during OGTT is also important in the diagnosis of impaired glucose intolerance (5). In the present study, the reduction rate of FFA in the 1st hour of OGTT was slower in obese when compared with nonobese. Actually, a reduction

of 41% was observed in the nonobese and of 26% in the obese. This implies that obesity may cause glucose intolerance which cannot be detected simply by OGTT.

No statistically significant difference was observed in glycosylated Hb values between obese and non-obese subjects ($p > 0.05$) nor did these values correlate with BMI, FFA or total cholesterol/HDL-cholesterol ratios. Glycosylated Hb measurements are useful for assessment of long-term glycémie control but do not reflect recent changes in blood glucose levels. On the other hand, determination of the degree of glycation of serum proteins with shorter half-lives ranging from 17 to 20 days provides a useful measure of recent glycémie control. Fructosamine concentrations correlate well with fasting glucose and glycosylated Hb concentrations (15). Our results support these findings. We observed significant positive correlations between glycosylated Hb and fructosamine and between fasting glucose and fructosamine concentrations in obese and nonobese subjects (Table 3). Various factors other than glycosylated Hb and fasting glucose influence fructosamine concentrations: concentration and turnover of serum proteins (15,16,17), hypertriglyceridemia (18) and body mass index (19,20). It has been suggested that an alteration in the glycation reaction itself is responsible for the decrease in fructosamine levels in obese people (20). In our study, fructosamine levels were significantly lower in obese subjects when compared with nonobese (1.862 ± 0.283 and $2.6560.223$ mmol/L, mean \pm SD, obese and control respectively, $p < 0.01$). A significant negative correlation between BMI and fructosamine was noted in obese subjects ($r = -0.323$, $p < 0.05$) (Table 3).

These observations suggest that caution must be taken in interpreting glycémie control in relation to serum fructosamine concentrations in obese subjects. It may underestimate the degree of blood glucose elevation in these patients. Our data imply that in obese nondiabetic individuals, reduced response of FFA to glucose as is reflected by reduced decrements in plasma FFA after glucose administration may point out to an impairment in glucose tolerance which cannot be detected by the OGTT. Furthermore, high total cholesterol/HDL-cholesterol ratios in these obese subjects support an increase in the risk for atherosclerosis.

Obes bireylerde glukoz intoleransi ve kardiyovasküler hastalık riski

Son yıllarda, obesite, diyabet ve kalp-damar hastalıkları riski açısından giderek önem kazanan bir faktör olmaktadır. Bu çalışmanın amacı, obez kişilerde diyabet ve kalp-damar hastalığı riskini araştırmaktır. Nonobez, nondiyabetik 10 kontrol ile 19 obez nondiyabetik denekte açlık kan şekeri, glikozile hemoglobin (Ghb), fruktozamin düzeyleri

ile total kolesterol/HDL-kolesterol oranı ve oral glukoz tolerans testi sırasında serbest yağ asitlerinin glukoz yanıtı belirlenmiştir. Glikozile hemoglobin kolon kromatografisi ile, fruktozamin ve kolesterol kolorimetrik yöntemle, serbest yağ asitleri titrimetrik olarak ölçülmüştür. Kontrol grubunda GHb 5.320 ± 0.842 , obezlerde 5.639 ± 0.663 ($p > 0.05$), fruktozamin kontrollerde 2.656 ± 0.223 , obezlerde 1.862 ± 0.283 mmol/L ($p < 0.01$) olarak saptandı. Oral glukoz tolerans testinin 1.saatinde serbest yağ asitlerinde kontrollerde %41, obezlerde %26 oranında azalma olduğu gözlemlendi. Kontrollerde total kolesterol/HDL-kolesterol oranı 3.110 ± 0.731 , obezlerde 4.167 ± 1.231 olarak saptandı ($p < 0.05$). Sonuç olarak, nondiyabetik obez olgularda glukoz karşı serbest yağ asitlerinin azalışı glukoz intoleransı ve total kolesterol/HDL-kolesterol oranının yüksekliği de bu kişilerde artmış ateroskleroz riski görüşünü desteklemektedir. [TurkJMedRes 1995, 13(4): 147-150]

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