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Original Research Article

Surrogate Measures of Insulin Sensitivity in Type 2 Diabetic Patients Useful in Clinical Practice

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Abstract

Insulin resistance or reduced insulin sensitivity is a key pathogenetic defect of type 2 diabetes mellitus and well established cardiovascular risk factor. The determination of insulin sensitivity and identification of insulin resistant individuals could improve their cardiovascular prognosis by effective treatment. The aim of the study was to elucidate easily applicable in routine clinical practice surrogate measures of insulin sensitivity, determining the highest percent of its variation in type 2 diabetic patients (T2D pts). Sixty three T2D pts of mean age 52.0±8.7 yrs, in good glycaemic control (glycated hemoglobin 6.38±0.58%) on a diet and oral antidiabetic drugs, participated in a cross-sectional study. The quantification of insulin sensitivity was done by the "gold standard"- a manual hyperinsulinaemic euglycaemic clamp technique and expressed as a glucose disposal rate (M, mg/kg/min). Stepwise multiple linear regression analysis elucidated waist circumference (WC) as an independent predictor of insulin sensitivity in diabetic women explaining 50.5% of its variation. In diabetic men predictors of insulin sensitivity were WC and diastolic blood pressure explaining 60.4% of its variation. This study determined surrogate measures of insulin sensitivity which are easily applicable in routine clinical practice, allowing physicians to identify and treat patients with insulin resistance effectively for a reduction of cardiovascular risk.

Key words: Cardiovascular risk, Hyperinsulinaemic Euglycaemic Clamp Technique, Insulin Resistance, Insulin Sensitivity, Type 2 Diabetes Mellitus, Waist circumference

INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents a huge and increasing medical, social and economic burden leading to an increased cardiovascular mortality, impaired quality of life and enormous health cost. The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. T2DM comprises the majority of people with diabetes around the world and approximately a half of million people in Bulgaria (World Health Organization, 2016).

The 2001 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines give of T2DM status of "cardiovascular disease risk equivalent". It means that patients with T2DM have the same cardiovascular disease (CVD) risk as individuals with established CVD (Haffner et al.,1998; Malmberg et al., 2000; NCEP ATP III, 2001). Nowadays, T2DM is considered and treated as a CVD (Inzucchi et al., 2015). CVD risk is significantly increased beginning as early, as 15 years before the diagnosis of T2DM, and it is becoming higher in the years closer to the actual time of clinical diagnosis (Hu et al., 2002). In fact, at the time of diagnosis 50% of the patients already have some manifestations of CVD (Groop, 2000).

The main pathogenetic abnormalities of T2DM are

insulin resistance or reduced insulin sensitivity and impaired insulin secretion but their relative contribution to the development of hyperglycaemia may differ due to heterogenety of the disease. In most of the patients with T2DM insulin resistance, generally defined as a subnormal tissue response to normal insulin concentration, is the leading defect, in the others that is impaired insulin secretion (Moller and Flier, 1991; Groop, 2000). Insulin resistance is considered as one of the most important of the possible antecedents of CVD, as well. Creating the concept of "syndrome X", Gerald Reaven was the first to hypothesize that tissue resistance to insulin action is a central feature for the development of T2DM and CVD (Reaven, 1988). Insulin resistance defined with the "gold standard" hyperinsulinaemic euglycaemic clamp technique or with its surrogate measure homeostasis model assessment of insulin resistance (HOMA-IR) is a necessary requirement in the definitions for the metabolic syndrome of World Health Organization and European Group for the Study of Insulin Resistance (Alberti and Zimmet, 1998; Balkau and Charles, 1999).

Correctly identifying patients with insulin resistance may, therefore, be clinically useful for prevention of CVD risk. The main determinants of insulin sensitivity are insulin mediated glucose disposal in peripheral tissues, mainly skeletal muscles, and insulin mediated suppression of hepatic glucose production. Hyperinsulinaemic euglycaemic clamp technique is the "gold standard" for measurement of in-vivo insulin sensitivity, however, its application in clinical practice is limited by a complex methodology requiring to be performed (De Fronzo et al.,1979). Precise measurement of insulin sensitivity/insulin resistance, is therefore, labour extensive, time consuming and expensive, unsuitable for routine clinical practice and population studies. To calculate HOMA-IR, a fasting blood sample for glucose and insulin has to be taken (Matthews et al., 1985). Consequently a number of more attractive and simple clinical methods have been developed.

Data about predictors of insulin sensitivity are controversial. That is because insulin resistance has multifactorial origin in which both genetic and environmental factors are thought to be involved. The established determinants of insulin sensitivity are different on the basis of the ethnicity and clinical characteristics of the subjects, the eographic region where they live and the life style factors such as dietary habits, fitness level, smoking and alcochol consumption. They are not universally accepted, but valid for certain population (Blonk et al., 1994; Carey et al., 1996; Bonora et al., 2002; Miyazaki et al., 2002; Wahrenberg et al., 2005; Mamtani et al., 2013; Cakir et al., 2016; Huth et al., 2016; Lalia et al., 2016).

The aim of the study was to elucidate easily applicable in routine clinical practice surrogate measures of insulin sensitivity, determining the highest percent of its variation in type 2 diabetic patients (T2D pts).

MATERIALS AND METHODS

Study participants

Sixty three T2D pts of mean age 52.0±8.7 yrs, mean duration of the diabetes 4.8±3.9 yrs, in good glycaemic control on a diet and oral antidiabetic drugs, defined by mean glycated hemoglobin (HbA1c) 6.38±0.58% participated in a cross-sectional study. The characteristics of T2D pts according to the sex is presented in Table 1.

The patients were hospitalized at the Department of Diabetology of Clinical Center of Endocrinology and Gerontology three days prior to the study to perform a case history, physical examination, biochemical investigations and glucose clamp study. They were advised to keep their diet, physical activity, diabetes and concomitant medication constant. Anthropometric, clinical, and biochemical parameters were determined before clamp study. Body Mass Index (BMI) was calculated as body weight (kg) divided by squared height (m^2). Waist circumference (WC) was measured using a non-elastic tape to the nearest 0.1 cm in the middle between lowest rib and the iliac crest in inspiration and expiration position and the mean value was taken. Hip circumference was measured at the level of the maximal circumference over the buttocks. Waist-to-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured with the use of manual sphygmomanometer on the left arm in a sitting position after at least 10 min of rest. Mean value was determined from two independent measurements with a 3 min interval between readings.

The patients had been informed about the aim of the study and written informed consent was obtained from all participants. The study protocol was approved by the local Ethical Committee of the Clinical Center of Endocrinology and Gerontology.

METHODS

Manual Hyperinsulinaemic Euglycaemic Clamp Technique

Insulin sensitivity was measured using a "gold standard"- a manual hyperinsulinaemic euglycaemic clamp technique. It was performed at 8.0 AM after a 12-hour overnight fast. An indwelling catheter was inserted in antecubital vein for infusion of insulin and glucose. A second catheter was placed in a dorsal hand vein in the contralateral arm for intermittent blood glucose and insulin sampling. The hand was warmed with heating pad

Table 1. Characteristics of type 2 diabetic patients according to the sex (mean±SD); HbA1c = glycated hemoglobin; HDL= high density lipoprotein; LDL= low density lipoprotein

Variables	Men	Women	p
Number	**29**	**34**	
Age (yrs)	51.3±8.5	52.6±9.0	ns
Body Mass Index (kg/m^2)	28.9±4.9	33.8±6.5	<0.01
Waist Hip Ratio	0.94±0.07	0.87±0.07	<0.001
Waist circumference (cm)	101.5±13.6	102.1±15.8	ns
Systolic blood pressure (mmHg)	141±28	153±25	ns
Diastolic blood pressure (mmHg)	92±16	99±15	ns
Fasting plasma insulin (mIU/l)	13.62±9.13	16.04±10.37	ns
Fasting plasma glucose (mmol/l)	6.86±1.30	6.88±0.98	ns
Postprandial plasma glucose (mmol/l)	7.78±1.69	7.26±1.48	ns
Hb A1c (%)	6.27±0.55	6.43±0.60	ns
Triglycerides (mmol/l)	2.09±1.30	2.13±1.33	ns
Total cholesterol (mmol/l)	5.22±0.93	5.83±1.88	ns
HDL cholesterol (mmol/l)	1.05±0.38	1.16±0.48	ns
LDL cholesterol (mmol/l)	3.22±0.99	3.54±1.21	ns
Uric acid (µmol/l)	324±77	307±103	ns

to arterialize the blood. A 50 ml insulin infusate (Actrapid HM, 100 U/ml, Novo Nordisk, Denmark) was prepared in isotonic saline at a concentration of 1U/ml and was infused by an infusion pump (Fresenius Kabi, Sweden). After obtaining the baseline samples for glucose and insulin, a priming insulin infusion was started to decline plasma glucose concentration to 5 mmol/l, followed by a constant insulin infusion of 40 mU/ m^2 body surface area/min for 120 min. Plasma glucose concentration was kept constant at a level of 5 mmol/l by 20 % glucose infusion (B. Braun infusion pump, Germany) added after decrease of blood glucose to 5 mmol/l. The adjustment of glucose infusion rate was done manually according to the plasma glucose level measured at 5 min intervals. Blood samples for determining plasma insulin concentration were drawn at 100, 110 and 120 minutes of the clamp study. Steady state plasma glucose and plasma insulin concentrations were calculated as the mean of the values obtained between 90 and 120 minutes of the clamp study. Under steady state conditions of hyperinsulinaemia and euglycaemia, endogenous insulin secretion and hepatic glucose production are suppressed and glucose infusion rate equals glucose disposal rate mainly in skeletal muscles. Insulin sensitivity was calculated from the amount of glucose infused during the last 30 min of the clamp study, when the plasma glucose concentration and glucose infusion rate were stable (steady state) and expressed as the amount of glucose metabolized (glucose disposal rate) per kg body weight per min (M; mg/kg/min) (De Fronzo et al.,1979; Kamenova, 2006).

Analytical Methods

Plasma glucose concentration was measured by a glucose oxidase method (Beckman Glucose Analyzer, USA). The concentration of HbA_1c (%) was measured after haemolysis (Cobas Integra System) via the immunoturbidimetric method using monoclonal antibodies attached to latex particles with a commercial kit (Roche Diagnostics, Germany). Blood samples for plasma insulin were immediately centrifuged and stored at -20° C until analysis. Plasma insulin concentration was measured by a Microparticle-Enzyme Immunoassay (MEIA Insulin, IMX System, Abbott, USA, reference range-2-25mIU/l,

Table 2. Correlations between insulin sensitivity (M) and cardiovascular risk markers in diabetic men and diabetic women (Pearson correlation analysis); HDL= high density lipoprotein

Cardiovascular risk markers	Insulin sensitivity (M)			
	Men		Women	
	r	p	r	p
Waist circumference	-0.700	<0.001	-0.702	<0.001
Body Mass Index	-0.681	<0.001	-0.658	<0.001
Waist Hip Ratio	-0.472	0.010	-0.399	0.019
Systolic blood pressure	-0.381	0.041	-0.517	0.001
Diastolic blood pressure	-0.410	0.027	-0.513	0.002
Fasting plasma insulin	-0.598	0.001	-0.340	0.049
Fasting plasma glucose	-0.381	0.041	-0.088	ns
Triglycerides	-0.272	ns	-0.517	0.002
Triglycerides/HDL-cholesterol	-0.210	ns	-0.386	0.027
Uric acid	-0.101	ns	-0.376	0.045

Table 3. Stepwise multiple linear regression analysis of dependence of insulin sensitivity (M) on waist circumference in diabetic women

Coefficients [a]					
	Unstandardized Coefficients		Standardized Coefficients		
Model	B	Std. Error	Beta	t	Sig.
(Constant)	11.695	1.648		7.096	0.000
Waist circumference	-8.242E-02	0.016	-0.710	-5.146	0.000
R^2 for total model (%)	50.5				

[a] Dependent variable: insulin sensitivity (M)

Laboratory of Radioimmune Assay, Clinical Center of Endocrinology and Gerontology). Serum levels of total cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides were defined by enzymatic method with a commercial kit (Roche Diagnostics) on biochemical analyzer Cobas Mira Plus, Switzerland, Clinical Laboratory, Clinical cener of Endocrinology and Gerontology). Low density lipoprotein (LDL) cholesterol was calculated by Friedewald equation.

Statistical Methods

Statistical analysis was done using statistical package for social science (SPSS, version 14 for Windows, Chicago, IL, USA). For descriptive purposes mean±standard deviation (SD) values are given. Analysis of variance (ANOVA) was used to determine statistically significant differences of study parameters between T2D men and T2D women. Pearson correlation analysis was used to determine correlation between insulin sensitivity (M) and cardiovascular risk markers. A p value <0.05 was considered as significant level of difference. Stability of the clamp studies was assessed by the coefficient of variation of mean plasma glucose (0-120 min) and steady state plasma glucose (90-120 min). Stepwise multiple linear regression analysis was used with insulin sensitivity (M) as dependent variable and cardiovascular risk markers as independent variables.

RESULTS

During the clamp studies a mean plasma glucose (0-120 min) was 5.001±0.197 mmol/l with a coefficient of variation 4% and a steady state plasma glucose (90-120 min) was 5.049±0.197 mmol/l with a coefficient of variation 2.6%. Steady state (90-120 min) plasma insulin was increased to a level of 84.7±33.3mIU/l, that has been shown to be able to suppress endogenous insulin secretion and hepatic glucose production (Groop, 2000). Under these steady state conditions of euglicaemia and hyperinsulinaemia, glucose infusion rate is equal to a glucose uptake from all the tissues in the body and it is a measure of tissue sensitivity to exogenous insulin expressed as a glucose disposal rate (M, mg/kg/min). Insulin sensitivity of the diabetic women M: 3.228±1.749 mg/kg/min was significantly lower compared to that of the diabetic men M: 4.761±3.428 mg/kg/min, p<0.05. The significant correlations between insulin sensitivity and cardiovascular risk markers in both sexes is presented in Table 2.

Table 4. Stepwise multiple linear regression analysis of dependence of insulin sensitivity (M) on waist circumference and diastolic blood pressure in diabetic men

Coefficients [a]					
	Unstandardized Coefficients		Standardized Coefficients		
Model	B	Std. Error	Beta	t	Sig.
(Constant)	28.349	3.793		7.474	0.000
Waist circumference	-0.168	-0.031	-0.664	-5.356	0.000
Diastolic blood pressure	-7.136E-0.2	0.026	-0.341	-2.750	0.011
R^2 for total model (%)	60.4				

Stepwise multiple linear regression analysis with insulin sensitivity (M) as a dependent variable and cardiovascular risk markers-BMI, WHR, WC, SBP, DBP, fasting plasma glucose, postprandial plasma glucose, HbA1c, triglycerides, total cholesterol, high density lipoprotein (HDL) cholesterol, atherogenic index triglycerides/HDL chiolesterol ratio, low density lipoprotein (LDL) cholesterol and uric acid as independent variables elucidated WC as an independent predictor of insulin sensitivity in diabetic women, explaining 50.5% of its variation. By WC mean M: 3.281 mg/kg/min with standard deviation: 1.301 was determined via the following equation: M =11.695-[0.08242 x WC (cm)] (Table 3).

In diabetic men predictors of insulin sensitivity were WC and DBP explaining 60.4% of its variation. By WC and DBP mean M: 4.761 mg/kg/min with SD: 2.758 was determined via the following equation:

M=28.349-[0.168 x WC (cm)]-[0.07136 x DBP (mmHg)] (Table 4).

DISCUSSION

In diabetic women insulin sensitivity, measured with the “gold standard” hyperinsulinaemic euglycaemic clamp technique and expressed as a glucose disposal rate (M) was significantly negatively correlated with WC, BMI, WHR, SBP, DBP, fasting plasma insulin, triglycerides, atherogenic index triglycerides/HDL cholesterol ratio and uric acid. Among these cardiometabolic risk markers, multiple linear regression analysis revealed as an independent predictor of insulin sensitivity (M) WC, as a measure of visceral adiposity, explaining 50.5% of its variation. In diabetic men insulin sensitivity (M) was significantly negatively correlated with WC, BMI, WHR, SBP, DBP, fasting plasma insulin and fasting plasma glucose. Multiple linear regression analysis revealed as an independent predictor of insulin sensitivity (M) WC and DBP explaining 60.4% of its variation. Interestingly, an widely used HOMA-IR was found to define 31.2% and 46.2% of the variation of insulin sensitivity in diabetic women and diabetic men, respectively (Kamenova et al., 2004).

Visceral obesity is linked to an increased risk of T2DM and CVD. Visceral adiposity has been demonstated as an indicator of insulin resistance. Under most circumstances, insulin resistance is the earliest detectable defect in pre-diabetic individuals but it is not known whether this is the primary defect or secondary to abdominal obesity with excessive free fatty acid turnover and increased lipid deposits in muscle. A strong correlation between abdominal obesity and insulin resistance has been observed. Japanese study shows that visceral adipose tissue, quantified with magnetic resonance imaging is associated with both peripheral and hepatic insulin resistance in 62 T2D pts, independently of gender (Miyazaki et al., 2002). The decrease in insulin sensitivity observed with aging is driven primarily by age-related changes in the content and distribution of adipose tissue and is independent of chronological age. Visceral fat and intrahepatic lipid are independent negative predictors of peripheral insulin sensitivity, whereas whole-body oxygen uptake and intramyocellular lipid are positive predictors in humans (Lalia et al., 2016). Obesity, in particular abdominal obesity, adiposopathy and low physical activity have been shown as independent contributors to insulin resistance in men without diabetes (Huth et al., 2016). Visceral fat volume, BMI and WC are positively correlated with HOMA-IR and visceral fat volume is a better determinant of HOMA-IR than abdominal wall fat index (Cakur et al., 2016). By measuring regional adiposity with dual-energy X-ray absorptiometry and insulin sensitivity by euglycaemic hyperinsulinaemic clamp in 22 healthy women with risk factors for T2DM, is found a strong negative relationship between central abdominal fat and whole-body insulin sensitivity and nonoxidative glucose disposal, independent of total adiposity, family history of T2DM, and post gestational diabetes (Carey et al., 1996).

Studies have established that the most practical way to determine the presence of visceral obesity is through measurement of WC. WC has been shown as an independent predictor of T2DM (Wei et al., 1997; Haffner, 2000). WC is better predictor of T2DM than WHR (Wang et al, 2005). Data on 9019 white participants in the third National Health and Examination Survey demonstrate that WC is more closely linked to CVD risk factors than is

BMI (Zhu et al., 2002). Similarly to our data, in healthy volunteers, WC has emerged as a strong independent predictor of insulin resistance defined by HOMA-IR, accounting for more than 50% of its variation alone (Wahrenberg et al., 2005). WC is an independent predictor of insulin sensitivity in female sex, explaining 79% of its variation (Carey et al., 1996). In Mexican American Families is found that WC is an independent predictor of cumulative and future risk of T2DM and outperformed BMI when compared in a head-to-head fashion. High WC≥94.65 cm after adjusting for age and sex is also associated with fasting glucose, insulin and triglycerides levels and low high-density lipoprotein levels indicating a potential association with insulin resistance. Moreover, WC is specifically and significantly associated with insulin resistant T2D patients (Mamtani et al., 2013).

The established determinants of insulin sensitivity define around 50% of its variation that confirms the role of genetic factors and defines the necessity to be investigated for certain nationality (Blonk et al., 1994; Ferrannini et al.,1996; Reaven, 1999; Bonora et al., 2002; Wahrenberg et al., 2005). Data collected at 20 centers throughout Europe from 1,146 men and women with normal glucose tolerance, ranging in age from 18 to 85 years show that 50% of insulin sensitivity can explain by components of the insulin resistance syndrome (Ferrannini et al., 1996).

Overweight, central fat distribution, dyslipidaemia, hypertension and poor glycometabolic control are strong independent predictors of insulin resistance in T2DM (Blonk et al., 1994; Bonora et al., 2002; Miyazaki et al, 2002; Mamtani et al., 2013). Study in the Netherlands in 46 T2D pts elucidate percent body fat, waist-to-hip ratio (without measurement of WC) and resting energy expenditure as independent predictors of insulin sensitivity, explaining 44% of its variation (Blonk et al., 1994). In 45 Italian T2D pts undergoing glucose clamp studies, insulin-mediated total glucose disposal is independently and negatively associated with SBP, plasma triglycerides and HbA1c. The overall variability of total glucose disposal rate explained by these variables is 53% (Bonora et al., 2002).

CONCLUSION

The importance of insulin resistance as the main pathogenetic factor for development of T2DM and CVD requires implementation of clinical methods as surrogate measures of insulin sensitivity. Our study elucidates independent predictors of insulin sensitivity accessible and easily applicable in routine clinical practice. Simple measurement of waist circumference and diastolic blood pressure could enable Bulgarian physicians for detection and effective treatment of insulin resistant patients for a reduction of CVD risk.

Conflict of Interest

There is no conflict of interest to declare.

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