Internal Medicine 2018 vol. XV No. 2 - www.srmi.ro
10.2478/inmed-2018-0009

INSULIN RESISTANCE (IR) IN PATIENTS WITH TYPE 2 DIABETES MELLITUS. IDENTIFYING PREDICTORS OF INSULIN RESISTANCE AND ESTABLISHING A CORRELATION BETWEEN INSULIN RESISTANCE AND CARDIOVASCULAR RISK

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Abstract
Insulin resistance is a determinant factor for the increased prevalence of hypertension and dyslipidemia in type 2 diabetes patients. In this study we determined those modifications of clinical and biochemical parameters associated with insulin resistance in the diabetic patient, these alterations can offer us indications concerning the pathophysiological mechanisms that lead to the diabetes development in the case of most patients. Also we determined a correlation between insulin resistance and cardiovascular risk, through the combined effect of age and insulin resistance on this risk.
Keywords: *insulin resistance, diabetes, cardiovascular risk.*

Rezumat
Rezistența la insulină este un factor determinat pentru prevalența crescută a hipertensiunii arteriale și a dislipidemiei la pacienții cu diabet zaharat tip 2. În acest studiu am determinat acele modificări ale parametrilor clinici și biochimici asociate cu o rezistență crescută la insulină la pacientul diabetic, aceste modificări putând oferi relații importante despre mecanismele fizopatologice care au dus la apariția diabetului la majoritatea pacienților. Deasemena am stabilit o corelație între insulinorezistență și riscul cardiovascular, prin impactul combinat al vârstei și rezistenței la insulină asupra acestui risc .
Cuvinte cheie: *rezistența la insulină, diabet, risc cardiovascular.*

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Introduction

Type 2 diabetes represents 80-90% of the total cases of diabetes. The disease is heterogeneous because in some patients there is a predominance of insulin resistance while in others there is an incapacity of β-pancreatic cells to produce insulin. Type 2 diabetes appears mostly in obese patients, where the pathophysiological mechanism is insulin resistance, as the excess of adipose tissue generates the production of toxic products that alter the insulin signaling pathway[1]. Insulin resistance leads to hypertension and dyslipidemia. Insulin resistance at the level of the endothelium determines the decrease of nitric oxide production which alters vasodilatation[2]. At the level of the adipose tissue insulin resistance determines the activation of hormone sensitive lipase which generates an increased level of free fatty acid generation. These free fatty acids lead to increased triglyceride synthesis in the liver, increased VLDL synthesis for triglycerides transport, and alteration of the composition of LDL and HDL, with generation of small dense LDL particles and rapid depletion of HDL. These pathophysiological mechanisms generate the pro-atherogenic dyslipidemia specific for type 2 diabetes[3]. Atherosclerosis is more severe in diabetes patients, which explains the increased number of vascular complications. The macrovascular complications in diabetes are represented by myocardial infarction, stroke and peripheral artery disease. In diabetes patients myocardial infarction risk is 2.13 fold higher for men and 2.95 fold higher for women than in population without diabetes[4].

Material and methods

In the study were included 121 newly-diagnosed diabetic patients. The inclusion criteria were: patients over 18 years of age, immediately after diabetes diagnosis, not receiving and antidiabetic therapy and patients that did not take any lipid lowering medications in the past 6 months. In all the patients we determined their BMI, abdominal circumference, blood pressure, serum lipid concentrations and their resistance to insulin by calculating HOMA-IR (Homeostatic Model Assessment of Insulin Resistance). Also for every patient we calculated their cardiovascular risk using UKPDS risk engine. The cut-off value for HOMA-IR was 2.5, higher values were considered as significant for insulin resistance, based on data provided by previous studies[5].

Results and discussion

Out of the 121 patients, 44 had a HOMA-IR<2.5 and were classified as non-insulin resistant and 77 had a HOMA-IR ≥2.5 and

Variable	Count	Mean SBP
TAS Non-IR	**44.00**	**131.34**
TAS IR	**77.00**	**135.82**

Table 1. *Mean value of SBP (mmHg) according to HOMA-IR*

Variable	Count	Mean DBP
TAD Non-IR	**44.00**	**81.36**
TAD IR	**77.00**	**83.29**

Table 2. *Mean value of DBP (mmHg) according to HOMA-IR*

Variable	Count	Mean BMI
IMC Non-IR	**44.00**	**24.80**
IMC IR	**77.00**	**28.60**

Table 3. *Mean value of BMI (kg/m2) according to HOMA-IR*

Variable	Count	Mean HbA1C
HbA1C Non-IR	**44**	**7.6864**
HbA1C IR	**77**	**8.0273**

Table 4. *Mean value of HbA1C (%) according to HOMA-IR*

were classified as insulin resistant. Patients with insulin resistance, HOMA-IR ≥ 2.5, had a mean systolic blood pressure of 135.82 mmHg, significantly ($p<0.01$) higher than patients without insulin resistance, HOMA-IR<2.5, that had a mean systolic blood pressure of 131.34 mmHg. These results correspond with data from literature demonstrating that insulin resistance influences blood pressure values[2].

Insulin resistant patients had a mean diastolic blood pressure of 83.29 mmHg, significantly ($p<0.01$) higher than insulin sensitive patients, that had a mean diastolic blood pressure of 81.36 mmHg. Insulin resistant newly diagnosed diabetes patients had a mean body mass index of 28.6 kg/m^2 significantly ($p<0.01$) higher than patients without insulin resistance, who had a mean body mass index of 24.80 kg/m^2. Patients with insulin resistance had a mean HbA1C of 8.02%, significantly ($p<0.01$) higher than patients without insulin resistance, who had a mean HbA1C of 7.68%. These results are not surprising because the effect of insulin resistance is reduced glucose transportation inside the cells and as a consequence hyperglycemia. All lipid parameters were significantly modified in patients resistant to insulin. Insulin resistance was associated with higher triglycerides, total cholesterol and LDL-cholesterol and lower HDL-cholesterol values. These results correspond to the atherogenic dyslipidemia that is found in type 2 diabetes: high triglycerides, high LDL-cholesterol and low HDL-cholesterol[3]. Also the Triglycerides/HDL-cholesterol ratio was significantly higher in insulin resistant diabetes patients. The TRIG/HDL-cholesterol ratio is recognized as a predictor of insulin resistance by numerous studies[6]. Data from literature indicates that TRIG/HDL-cholesterol ratio accurately identifies insulin resistant individuals and those who have an increased cardiometabolic risk[5]. The cut-off value of TRIG/HDL-cholesterol ratio for predicting insulin resistance is 2.27[7]. In our study patients both insulin resistant and non-insulin resistant had higher TRIG/HDL-cholesterol ratio than the cut-off value indicated in the literature, but both groups of patients had dyslipidemia although in the insulin resistant ones it was more severe. Non HDL-cholesterol was significantly higher in insulin resistant patients than in non-insulin resistant patients. Studies indicate that non HDL-cholesterol is a more accurate predictor than LDL-cholesterol for the prediction of increased level of small, dense LDL particles associated with atherosclerosis in diabetic patients[8].

Conclusion

Significant differences were recorded between insulin resistant and non-insulin resistant newly diagnosed diabetes patients. Insulin

Variable	Count	Mean
Triglyicerides Non-IR	**44.00**	**151.45**
Triglycerides IR	**77.00**	**188.49**
Cholesterol Non-IR	**44.00**	**190.99**
Cholesterol IR	**77.00**	**196.57**
LDL-cholesterol Non-IR	**44.00**	**118.51**
LDL-cholesterol IR	**77.00**	**123.39**
HDL-cholesterol Non-IR	**44.00**	**48.21**
HDL-choelsterol IR	**77.00**	**47.22**

Table 5. *Mean values of triglycerides, cholesterol, LDL-cholesterol and HDL-cholesterol (mg/dl) according to HOMA-IR*

Variabila	Count	Mean
TRIG/HDL-cholesterol Non-IR	**44.00**	**3.53**
TRIG/HDL-choelsterol IR	**77.00**	**4.36**

Table 6. *Mean TRIG/HDL-ratio according to HOMA-IR*

Variable	Count	Mean
Non HDL-colesterol Non-IR	**44.00**	**142.78**
Non HDL-coelsterol IR	**77.00**	**149.35**

Table 7. *Mean non-HDL according to HOMA-IR*

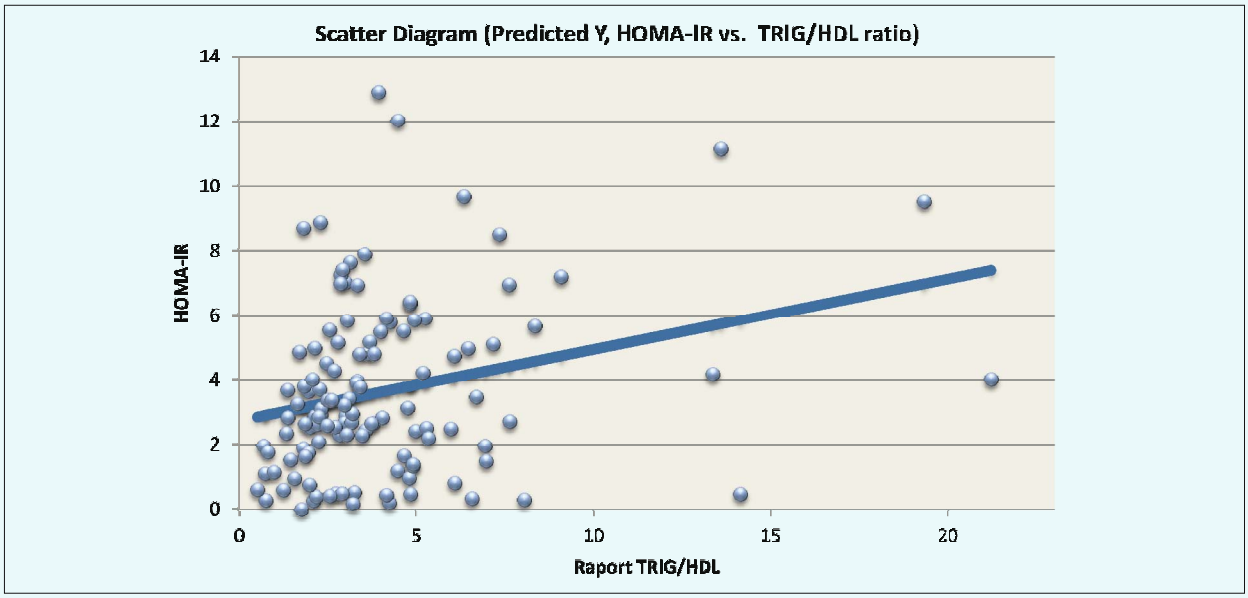

Figure nr. 1. *Prediction of HOMA-IR using TRIG/HDL-ratio*
TRIG/HDL-ratio accurately predicted HOMA-IR level in newly diagnosed diabetes patients (p=0.036).

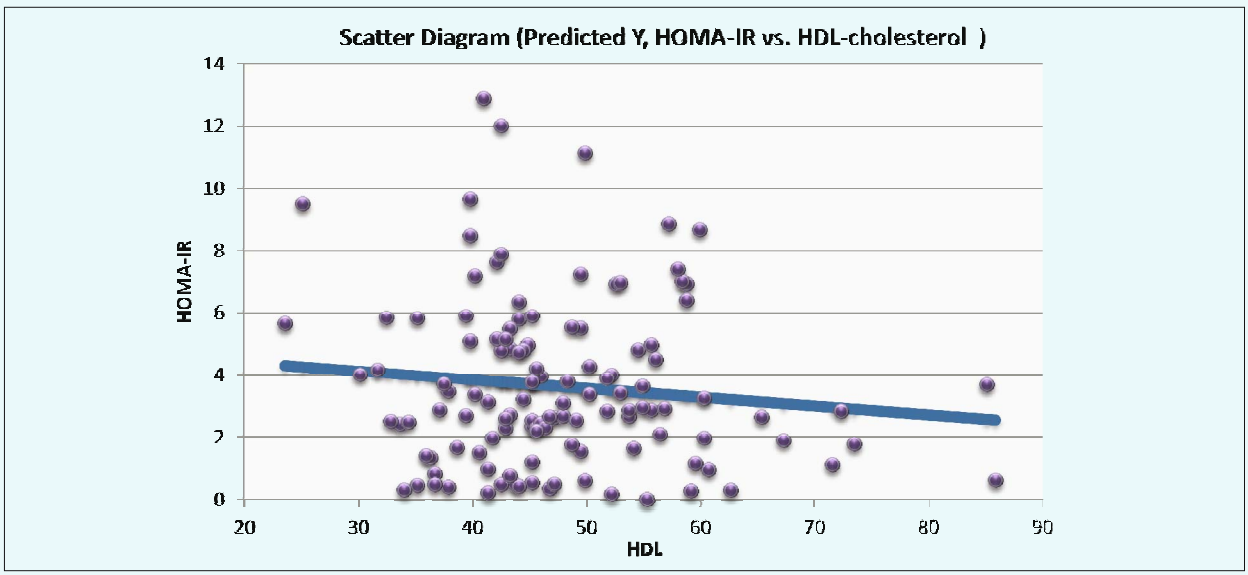

Figure nr. 2. *Prediction of HOMA-IR using HDL-cholesterol levels*
HDL-cholesterol did not correlate with HOMA-IR (p=0.22). Despite this we can observe a descending trend higher level of HDL-cholesterol corresponding to lower level of HOMA-IR.

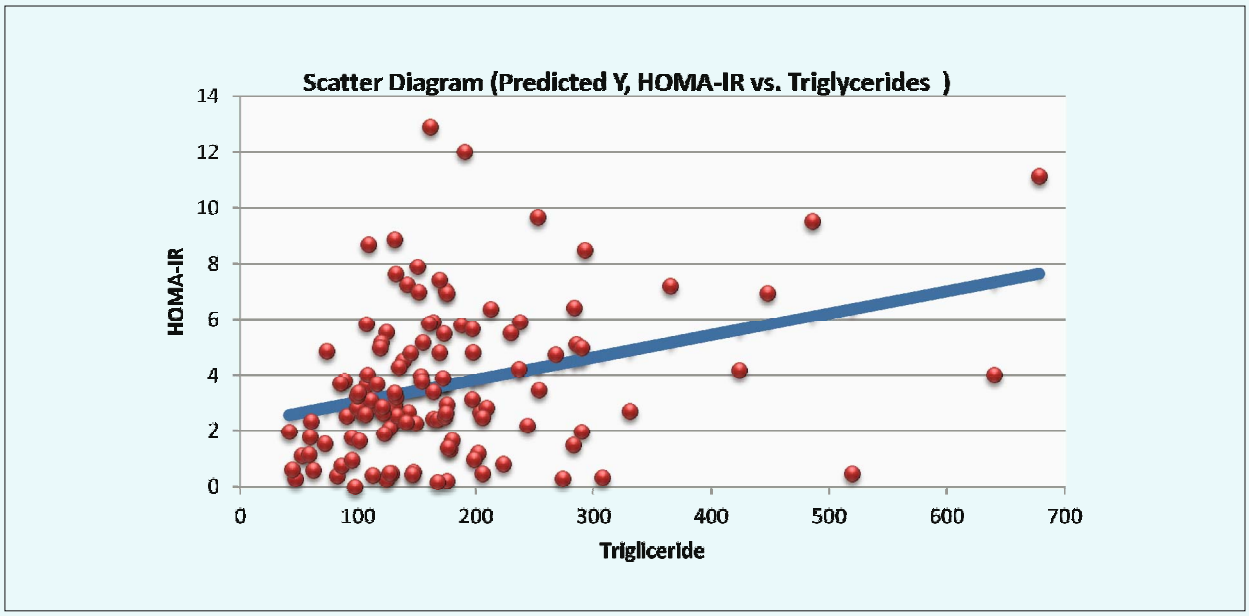

Figure nr. 3. *Prediction of HOMA-IR using triglycerides levels*
There is a strong correlation between triglycerides levels and HOMA-IR (p=0.0004), higher levels of triglycerides corresponding to a high level of insulin resistance.

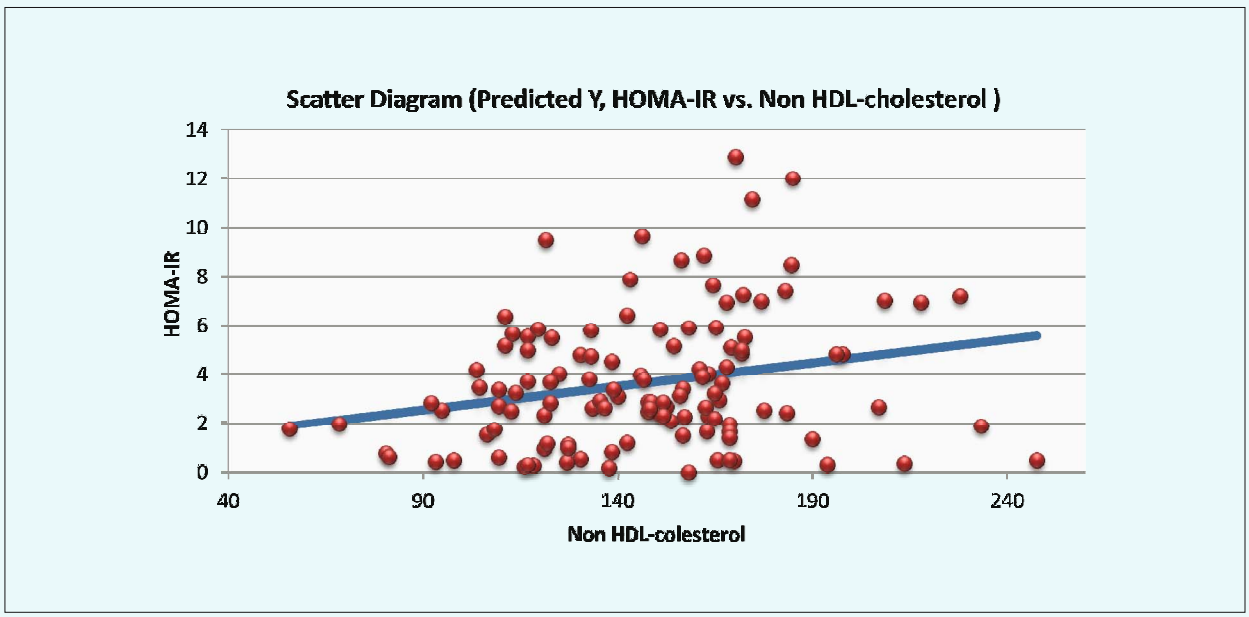

Figure nr. 4. *Prediction of HOMA-IR using non HDL-cholesterol values*
There was a strong correlation between non HDL-cholesterol levels and HOMA-IR (p=0.008). High levels of non HDL-cholesterol correspon

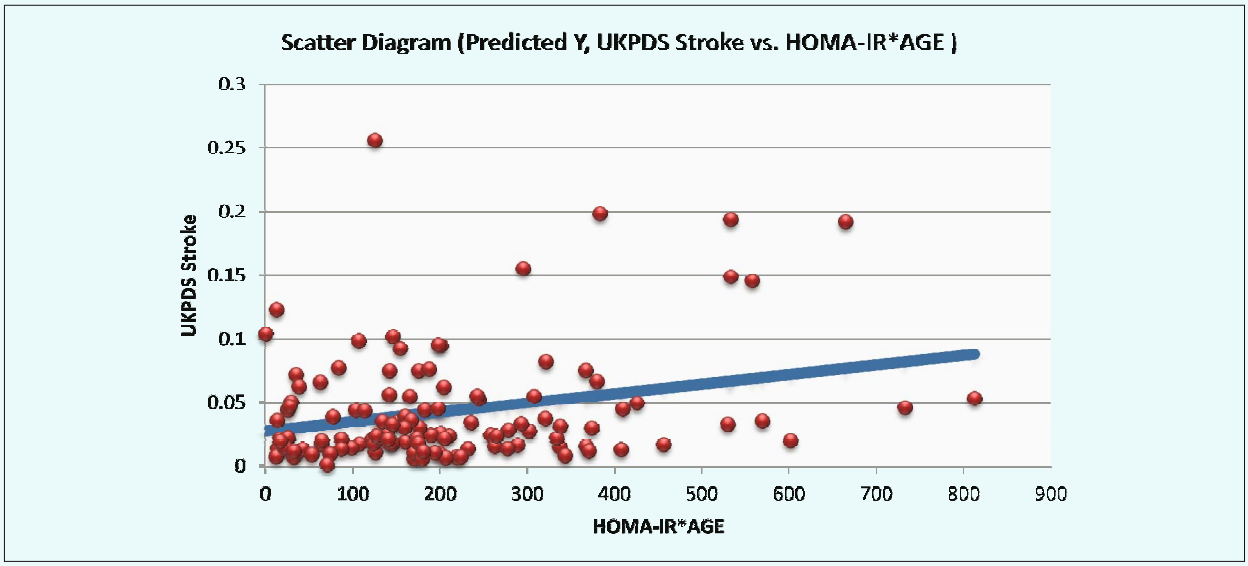

Figure nr. 5. *Prediction of coronary heart disease risk at 10 years using HOMA-IR*AGE score*
There was a significant correlation between age multiplied by insulin resistance and coronary heart disease at 10 years calculated by UKPDS risk engine (p<0.05).

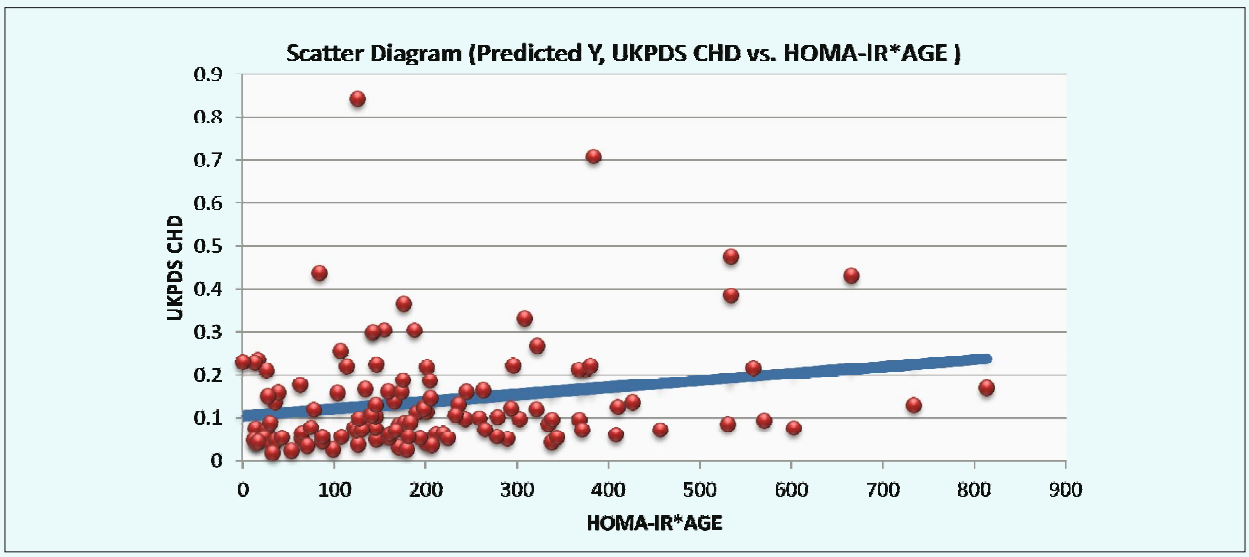

Figure nr. 6. *Prediction of cerebrovascular disease risk at 10 years using HOMA-IR*AGE score*
There was a significant correlation between age multiplied by insulin resistance and cerebrovascular disease risk at 10 years calculated by UKPDS risk engine (p<0.05).

resistance, defined by HOMA-IR ≥2.5, is associated with higher systolic and diastolic blood pressure, higher BMI, higher HbA1C, higher levels of total cholesterol, LDL-cholesterol, triglycerides and lower levels of HDL-cholesterol. Also newly diagnosed diabetes patients with HOMA-IR ≥2.5 had higher TRIG/HDL-cholesterol ratio, and higher non HDL-cholesterol than patients with HOMA-IR <2.5. The parameters that correlated with insulin resistance were: triglycerides, TRIG/HDL-cholesterol ratio and non HDL-cholesterol, meaning that they can be used as predictors of insulin resistance.

HOMA-IR did not correlate with coronary heart disease and cerebrovascular disease risk at 10 years calculated using UKPDS risk engine. However after assessing the cumulative impact of insulin resistance and ageing with a simple score HOMA*AGE we obtained a statistically significant correlation with coronary heart disease and cerebrovascular disease risk at 10 years. These results show that insulin resistance has an increased severity with advanced age. Based on this results construction of future cardiovascular risk scores is possible based on insulin resistance.

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