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UPOTREBA INDEKSA ZA PROCENU POREMEĆAJA GLIKOREGULACIJE I KARDIOMETABOLIČKOG RIZIKA

USE OF INDICES FOR THE EVALUATION OF GLUCOREGULATORY IMPAIRMENTS AND THE ASSESSMENT OF CARDIOMETABOLIC RISK

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Abstract

The increasing incidence of metabolic syndrome represents one of the biggest health problems in today's world and a risk factor for the occurence of other serious diseases. Insulin resistance is one of the crucial components of the metabolic syndrome and as such it requires an adequate and prompt diagnosis. Different indices based on laboratory and anthropometric parameters can be used to estimate the level of insulin resistance. The aim of this paper is to highlight the diversity and importance of these indices in the early detection of latent impairments in glucose metabolism and the assesment of cardiometabolic risk. Calculating some of the indices requires determining insulin level, lipid panel and anthropometric parameters. Indices that use glycemia and insulinemia are HOMA, QUICKI, Matsuda and Stumvoll indices. Indices that use a combination of glucoregulatory and lipid panel parameters to assess the degree of insulin resistance are the TyG and McAuley. VAI and LAP indices use lipid panel and anthropometric values to estimate the cardiometabolic risk. Using these indices together, we get a better insight into the impairments in glucose metabolism which may allow us to prevent the development of complications stemming from the metabolic syndrome.

Glucoregulation impairment and the metabolic syndrome

Metabolic syndrome encompasses a wide variety of conditions, such as: abdominal obesity, increased levels of cholesterol and triglycerides, insulin resistance and arterial hypertension.(1) It increases the risk for developing several non-communicable chronic diseases, including type 2 diabetes (T2D), cardiovascular disease, cerebrovascular disease and cancer.(2,3) Also, deficiencies in vitamin B12 and vitamin D are commonly found in obesity and type 2 diabetes.(4,5) Given the rising incidence of the metabolic syndrome in the general population, the focus has shifted towards detecting the metabolic impairments present in obesity before the development of chronic disease.

Nowadays, the insulin resistance is diagnosed at an ever-increasing rate, not only in obesity, but also in other conditions such as polycystic ovary syndrome (PCOS).(6) The problem with diagnosing insulin resistance is the presence of many different indices and their improper use. Some of the indices use only the fasting insulinaemia and glycemia, others include the oral glucose tolerance test (OGTT) values of both insulinaemia and glycemia, while another group combines lipid and glucoregulatory parameters. Physicians are therefore left with the tough choice, further complicated by the fact that the reference values of some indices are not well-defined or are not defined at all for the population in question.(7)

The aim of this paper is to highlight the importance and the diversity of indices used for detecting the potential impairments in glycoregulation and assessing the cardiometabolic risk. Also, we wish to open a discussion about the use of these indices in primary care, in order to establish the cut off values for these indices for our population.

Indices of glucoregulatory impairment and metabolic risk

Indices using glucoregulatory parameters

Starting in the 1980s, a lot of research has focused on creating a formula that can be used to detect and quantify the level of insulin resistance and secretion. A basic test for glucose metabolism evaluation is the OGTT. This test gives information about the fasting glycemia and the postprandial glycemia at 60, 120 and 180 minutes after the ingestion of 75 grams of glucose. (8) In addition, insulinaemia can also be measured in the same time points, providing additional information about our patient's glucoregulation.

The gold standard in the evaluation of insulin resistance and/or sensitivity is the euglycemic clamp technique. However, this procedure is too complicated to perform, rendering it suboptimal in a routine setting.(9) Based on the results of clamp measurements, Matthews et al. created a mathematical model and came up with the **HOMA indices**, which are able to estimate the level of insulin resistance and secretopm with relative accuracy. HOMA indices are derived from fasting glycemia and insulinaemia, either by using a formula (HOMA1) or by using an online calculator (HOMA2), created by the Oxford Centre for Diabetes, Endocrinology and Metabolism - www.dtu.ox.ac.uk. (10,11,12). Using the formula (HOMA1), it is possible to obtain parameters of insulin resistance (HOMA IR) and secretion (HOMA B), while using the calculator (HOMA2) produces an additional parameter – peripheral tissue insulin sensitivity (HOMA S). (10)

HOMA IR reference values need to be defined for each population, based on population studies.(7) Such a study, consisting of 486 participants and using the online calculator (HOMA2), was conducted in the Clinical Centre of Vojvodina and a cut off value of 2 for HOMA IR was defined. (12) It is important to note that this cut off value is valid only when using the online calculator. If HOMA IR is calculated using the formula, the values are higher.

Very similar to HOMA, **QUICKI index** (Quantitative Insulin Sensitivity Check) is another tool used to evaluate the degree of insulin sensitivity.(13)

There are also more complex insulin sensitivity indices which combine OGTT values (glycemia and insulinemia) with anthropometric and demographic parameters (BMI, waist circumference, age, sex...), such as Stumvol and Matsuda index. (14,15,16) Matsuda index is particularly interesting as it includes glycemias and insulinaemias measured at each time point of the OGTT. (16) Furthermore, in the original paper, Matsuda also presented the physiological curve for both glycemia and insulinaemia during the OGTT. The insulinaemia curve could be used as a guide for insulinemia during OGTT, since reference values are reported only for fasting insulinaemia. (16) However, we must point out that, in our population, cut off values for Matsuda and Stumvol index haven't been established; in Japanese population, values for Matsuda index below 4.3 are indicative of insulin resistance.(17)

Indices using lipid and anthropometric parameters

Representantives of this group are **Visceral Adiposity Index** (VAI) and **Lipid Accumulation Product** (LAP). They combine lipid levels with anthropometric and demographic variables in order to evaluate cardiometabolic risk.

Visceral Adiposity Index is calculated with a sex-specific formula. (18) This index includes waist circumference, body mass index and laboratory parameters such as triglyceride and HDL concentrations. There is also a separate index consisting only of triglyceride-to-HDL ratio that has proven to be equally as effective as fasting insulin in predicting insulin resistance. (19) A study by Amato et al. (18) concluded that VAI is a good indicator of visceral obesity and thus is more suitable for routine use in a clinical setting compared with trygliceride-to-HDL ratio. The amount of visceral fat tissue is a much more important factor in the development of insulin resistance. Also, visceral obesity might be present in people with low amounts of subcutaneous fat. Taking this into account, this index is considered to be important in assessing the risk of developing insulin resistance. (20) Calculating this index allows physicians to evaluate the risk for the development of metabolic syndrome, especially in obese patients.(21) It has also been shown that VAI is highly correlated with the degree of insulin resistance in patients suffering from polycystic ovary syndrome.(22) Furthermore, a study with more than 1000 participants found a significant inverse correlation between VAI and insulin sensitivity measured using the euglycemic clamp method.(18) Multiple studies had found a significant negative correlation between adiponectin levels and VAI, rendering VAI an useful tool in detecting fat tissue dysfunction.(23, 24)

LAP (Lipid Accumulation Product) index is calculated as the ratio between waist circumference and triglyceride concentration, making it easily applicable in clinical practice. LAP index also has a sex-specific formula. (25) In some newer studies, LAP index had been more precise than BMI in identifying people at risk of developing type 2 diabetes, as well as other complications of obesity.(26,27) Also, Chiang et al. found a significant positive correlation between LAP and the amount of visceral fat as well as the concentration of inflammatory cytokines.(28) Two studies found that LAP is a better predictor of HOMA IR compared with BMI and waist circumference.(29,30) Examining the link between LAP and various laboratory parameters, Mirmiran et al. found a significant correlation with fasting glycemia, lipoprotein levels, lipid peroxidation and oxidative stress (malonyldialdehyde – MDA), as well as high-sensitivity C-reactive protein. (31) This evidence suggests that VAI and LAP indices could be used for overall evaluation of health status in obese patients.

Indices using both glucoregulatory and lipid parameters

TyG and McAuley indices combine glucoregulatory and lipid parameters in order to estimate insulin resistance (TyG) or sensitivity (McAuley). The **TyG index** is calculated using triglycerides and fasting glycemia. (both concentrations

expressed as mg/dl).[32] A study by Navarro-Gonzalez et al. [33] had shown that the changes of TyG index are more useful in assessing the risk of development of type 2 diabetes than changes in body weight. Also, two studies found a significant correlation between the TyG index values and the euglycemic clamp test, as well as with the HOMA IR index. .[34, 35] **McAuley index** is an indicator of insulin sensitivity and includes fasting insulin and triglyceride levels. [36] According to the study by Ascaso et al., McAuley index was found to have the strongest correlation with the *Minimal Model test* (MMAMG) used to evaluate insulin sensitivity.[37]

Evaluation of inflammation

The inflammation present in obesity and metabolic syndrome can be evaluated by measuring the levels of certain inflammatory markers, such as interleukins and TNF-□. However, as these tests are expensive, a more commonly used marker in practice is the neutrophil-lymphocyte ratio. Increased levels of this ratio is positively correlated with the inflammatory markers and the risk of developing atherosclerosis, consequently leading to higher risk for cardiovascular, cerebrovascular and other diseases which are the result of chronic inflammation. [38] Also, the neutrophil-lymphocyte ratio had shown a high positive correlation with HOMA IR in type 2 diabetes patients.[39] Furthermore, this index was higher in type 2 diabetes patients with early signs of nephropathy compared with those without it. [40] On the other hand, one study concluded that the neutrophil-lymphocyte ratio is not a good predictor of inflammation and the severity of metabolic syndrome, stating that white blood count and high-sensitivity C-reactive protein are better predictors.[41]

CONCLUSION

Using different indices based on glucoregulatory parameters provides a better insight into the metabolic dysfunction in obese people compared with using any of the individual laboratory or anthropometric measurements. Lipid indices are very user-friendly which makes them appropriate for use in primary care. A more widespread use of indices that combine both glucoregulatory and lipid parameters could provide physicians with a chance to identify latent metabolic dysfunction in obesity which would lead towards a timely prevention of all of its complications.

Sažetak

Metabolički sindrom predstavlja veliki problem današnjice i rizik za nastanak brojnih ozbiljnih oboljenja. Jedna od najvažnijih komponenti metaboličkog sindroma je insulinska rezistencija, te je neophodna adekvatna i pravovremena dijagnostika ovog stanja. Za procenu insulinske rezistencije mogu se koristiti različiti indeksi koji koriste laboratorijske, ali i antropometrijske parametre. Cilj ovog rada jeste ukazivanje na raznovrsnost i značaj ovih indeksa u ranom otkrivanju latentnih poremećaja metabolizma glukoze i kardiometaboličkog rizika. Kao osnovni test za otkrivanje poremećaja glikoregulacije je oralni glukoza tolerans test. Izračunavanjem indeksa moguće je ranije otkriti poremećaje metabolizma glukoze, ali je u njihovom računanju neophodno uključiti više podataka poput nivoa insulina, lipidnog statusa, kao i antropometrijske parametre. Indeksi koji procenjuju glikoregulaciju a koriste podatke glikemije i insulinemije su HOMA indeksi, QUICK indeks, Matsuda i Stumvol indeksi. Pored toga postoje indeksi koji koriste podatke glikoregulacije kombinujući ih sa komponentama lipidnog statusa poput McAuley indeksa i TyG indeksa. Indeksi koji govore i o glikoregulaciji ali procenjuju i kardiometabolički rizik su VAI i LAP indeks. Kombinujući ove indekse stičemo daleko širu sliku o latentnim poremećajima metaboličkog sindroma, te se može mnogo više učiniti povodom prevencije oboljenja do kojih ovo stanje može dovesti.

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