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Επίκαιρο άρθρο

The metabolic syndrome is a really artificial concept

D. Karamitsos

Summary

Reaven in 1988 suggested that the constellation of diabetes or glucose intolerance, dyslipidemia and arterial hypertension (syndrome X initially and metabolic syndrome later) has a common etiology based in hyperinsulinemia and / or insulin resistance. It is well known that the above risk factors increase the liability to early atherosclerosis. Reaven's theory had soon obtained supporters and some pharmaceutical companies −for their own reasons− found the background to indirectly advertise their drugs which did not act via insulin secretion. The determination of specific diagnostic criteria for «metabolic syndrome» has been an endless procedure. The most polular diagnostic criteria are those that arouse from the ATP III, WHO, IDF and EGSIR classifications which included many variables and methods. By combining these variables you can reach a diagnosis of the «metabolic syndrome» in 11 different ways for the WHO, IDF and EGSIR and 16 for the ATPIII classification. Insulin resistance in diabetic patients indicate lack of the appropriate insulin secretion. In type 2 diabetes mellitus apart from insulin resistance a reduced insulin secretion exists. The latter constitutes a prerequisite for the development of disease. Attempts to correlate insulin per se with the end point of vascular diseases in diabetic subjects came without clear results. The so called metabolic syndrome can not be explained on a common pathogenetic background and is possibly a result of synergy between genetic and environmental factors. Interestingly, even Reaven has recently admitted that "there is no reason to believe that the metabolic syndrome exists as a distinct clinical entity".

Central obesity and insulin resistance

Central obesity is well correlated with insulin resistance. Moreover, obesity is related to many metabolic and hormonal changes. Theoretically some of these changes may be consequences of either obesity or insulin resistance or both. Fat tissue is a real endocrine gland that secretes a large number of substances which are related to the insulin resistance state (leptin, adiponectin, IL-6, TNF-a, resistin, TGF-β, steroids, PAI-1, IGF-1, and others). The majority of obese subjects, diabetic or not, display insulin resistance. Healthy individuals with insulin resistance need more insulin secretion to keep their blood glucose in normal levels. Diabetic subjects with insulin resistance have lower insulin secretion compared to normal subjects and this dysfunction of pancreatic beta-cells is responsible for diabetes mellitus. Obese subjects with normal blood glucose levels secrete more insulin than obese diabetic ones. Normal weight subjects have in fasting state lower insulin concentration than obese diabetic patients. This fact

A′ Propedeutic
Medical Department
Aristotle' s medical school
AHEPA Hospital
Thessaloniki

explains the false terminology of hyperinsulinemia. This designation has caused a lot of confusion and misunderstanding. For all the biochemical substances and hormones exists a scepticism about the determination of their normal values. If these variables are continuous, it is very difficult to figure out the cut off point between normal and abnormal concentrations. This difficulty, as far as blood glucose is concerned, is responsible for the need of the concept of impaired fasting glucose. Also, a difficult matter is it the normal range of plasma insulin, because its secretion depends on a variety of factors, such as plasma glucose, obesity and insulin resistance. Furthermore, sedentary life and stress increase the need for higher insulin secretion. High levels of fatty acids increase insulin resistance too. Patients with a genetic predisposition to dyslipidemia and increased VLDL, display deterioration of their lipid profile if diabetes is not well controlled. Obese subjects are characterized by higher levels of plasma cortisol, increased sympathetic drive, and increased incidence of arterial hypertension.

Reaven's theory

Reaven suggested that in «metabolic syndrome» (syndrome X in 1988) a common pathogenetic mechanism exists where hyperinsulinemia and/or insulin resistance is/are the key point[1]. Reaven because insulin is an anabolic hormone (with growth properties) considers that in «metabolic syndrome» insulin contributes to atherogenicity. Some experimental findings in isolated tissues —mainly by Stout[2]— supported Reaven's point of view. This theory soon earned many supporters, and some pharmaceutical companies —for their own reasons— found the background to advertise indirectly new drugs that had not any effect on insulin secretion. In medical literature «hyperinsulinemia» has been referred in an excessive way, although this term has recently been withdrawn and replaced by «insulin resistance» which is much more secure term and easy to be accepted. Searching «hyperinsulinemia» as a title word in Medline PubMed's database, we found only seven related papers. This number is extremely low despite the wide (unjustifiably) usage of the term "hyperinsulinemia" in the main text of papers. There is no usually justification for this designation. A limited number of researchers have defined hyperinsulinemia as the upper quadrant or upper tenth of insulin concentrations and attempted some correlations. However it is difficult to regulate and justify all the various factors that participate in the modulation of plasma insulin's concentration such as lipids, glucose, emotional stress, mood, physical exercise, inactivity, body weight, fat distribution in the body (central obesity) and others. As far as the diabetic subjects are concerned, efforts to correlate insulin with end point of vascular diseases did not reach clear conclusions[3].

Arterial hypertension

Arterial hypertension in cases of «metabolic syndrome» is not explained on a common pathogenetic background. Patients with true hyperinsulinemia as well as those suffering from insulinoma do not have hypertension. Most of dyslipidemic diabetic patients (high VLDL, low HDL) can have normal lipids after the achievement of optimal glucose control under insulin treatment. Many extremely obese insulin resistant patients do not exhibit any of the components of «metabolic syndrome» for many years. Actually, some of them may develop diabetes and /or hypertension at a later stage and may demonstrate increased lipids positively correlated with high plasma glucose.

Impaired insulin secretion

Insulin resistance in diabetic patients clearly indicates lack of (the) appropriate insulin secretion. In other words, as far diabetic patients are concerned, correlations between insulin resistance (measured by euglycemic insulin clamp technique) and various biological parameters are in fact correlations with the lack of insulin. Under this consideration the entire initial Reaven' s concept about hyperinsulinemia and its detrimental consequences is totally wrong. Some of the metabolic alterations could be attributed to hypoinsulinemia[4]. Lack of insulin is responsible for endothelial dysfunction and hypercoagulation which are well known predisposing factors to atheromatosis and thrombosis. Actually insulin possesses a number of antiatheromatic and antithrombotic properties and exhibits a protective role from atherosclerosis (Fig. 1).

Metabolic syndrome as an artificial entity

Insulin, after a period of wrong accusations, comes back and takes its revenge. The «metabolic syndrome» appears to be an artificial entity with no common pathogenetic background. In other words, the so called metabolic syndrome is nothing else

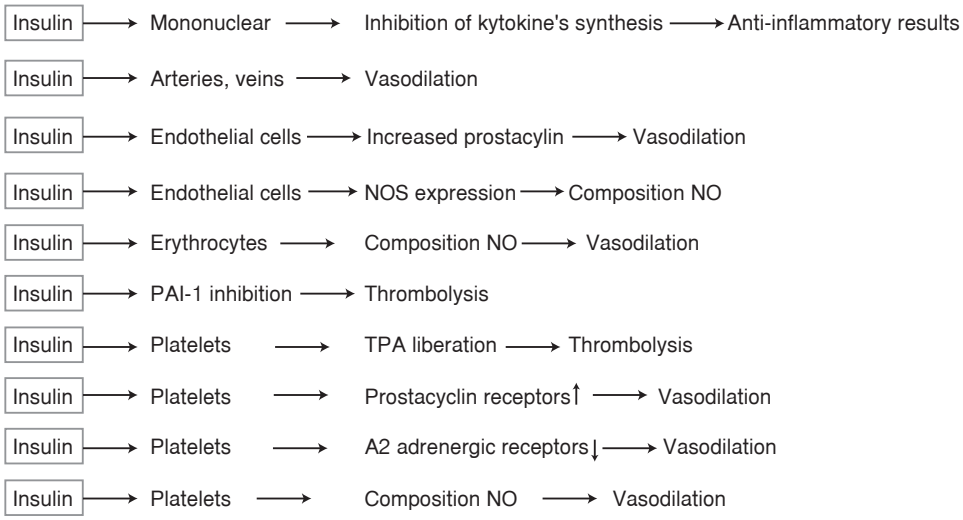

Fig. 1. *The antithrombotic and antiatheromatic actions of insulin.*

but a coincidence of various components that became very common in modern life over the last 100 years. These components –high plasma glucose, high VLDL and low HDL (triglycerides >150 mg/dl and /or HDL <40 mg/dl), obesity, arterial hypertension- have interrelationships[5], but this fact alone does not imply any common pathophysiology. I have expressed my doubts on the existence of «metabolic syndrome» as a clinical entity having common pathophysiology in an article published in Hellenic Diabetological Chronicle 14 years ago under the title «Syndrome X, myth or reality»[6]. Recently A.M. Gale came up with an editorial in Diabetologia under the meaningful title "The myth of metabolic syndrome"[7]. In the same issue an article was published with new ideas on the appraisal of «metabolic syndrome» rising many questions. As it is stated «While there is no question that certain CVD risk factors are prone to cluster, we found that the metabolic syndrome has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a CVD risk marker[8]. Clinicians should evaluate and treat all cardiovascular risk factors without taking into consideration whether a patient meets the diagnostic criteria of metabolic syndrome or not, because this diagnosis does not offer any further advantage. All components of the so called «metabolic syndrome» need to be treated anyway. The diagnosis of insulin resistance does not carry a greater risk than the constellation of any individual elements of «metabolic syndrome»[7,8].

The etiology of "metabolic syndrome"

The etiology of «metabolic syndrome» may be explained by the coexistence of various genes predisposing to obesity, diabetes, dyslipidemia, and arterial hypertension as well as environmental factors[9]. Attractively, this gene theory explains why all these components are not always presentt. Ninety three per cent of diabetic subjects display insulin resistance and 80% are obese. Only a small minority of them have all the components of «metabolic syndrome». However, there are many different ways according to many definitions to categorize a person in the group of «metabolic syndrome». The various criteria for the diagnosis of «metabolic syndrome» result in numerous combinations. For example, following the National Cholesterol Education Program's Adult Treatment Panel (ATP) III criteria, we can come with 16 possible combinations. However, with the WHO as well as with IDF and EGSIR criteria we have 11 possible combinations. So far, various other definitions have been proposed, in addition to the four ones which already been mentioned. Thereafter, it is clear that we do not have a universally accepted definition of the syndrome. The numerous combinations of the components of metabolic syndrome render it extremely multifarious (Table 1).

It is obvious that the criteria for the diagnosis of «metabolic syndrome» are arbitrary and the fact that there is a constant change of them reveal thoughts to overdiagnosis. We can say that the concept of «metabolic syndrome» may be due to some sort

Appendix

Table 1. Comparison of thevarious diagnostic criteria of metabolic syndrome

	WHO	IDF	EGSIR	NCEP ATP III
Requirements for diagnosis	BG or Ins Res Plus 2/7	Central obesity Plus 2/5	Ins Res (25% upper) Plus 2/5	At least 3 present
Central Obesity	W/h radio >0.9 M >0,85 F	Circumference >94 M >80 F	Circumference >94 M >80 F	Circumference >102 M >88 F
Blood Glucose	GI ↑ any	Gl >100 mg/dl	Gl >100 mg/dl	Gl >100 mg/dl
Blood Pressure	>140 mmHg >90 mmHg	>130 mmHg >85 mmHg	>140 mmHg >90 mmHg	>130 mmHg >85 mmHg
Triglycerides	>150 mg/dl	>150 mg/dl	>177 mg/dl	>150 mg/dl
HDL	<36 mg/dl M <38,6 mg/dl F	<40 mg/dl M <50 mg/dl F	<38,1 mg/dl	<40 mmHg
Insulin Resistance	Yes	Not refered	Yes	Not refered
Microalbuminuria	Yes Ratio Alb/creat >30	–	–	–
Year	1999	2005	1999	2001

M=male, F=Female, Gl=Glucose

of «conspiracy» or misunderstanding or both. Normal values for blood pressure and lipids are getting lower by the experts, as happens to the diagnostic criteria for metabolic syndrome, hence a great proportion of population in western countries will be diagnosed to have «metabolic syndrome». This fact has both therapeutic and economic implications in pharmaceutical industries and national health economies. Epidemiologically, syndrome X has been disputed by Jarret[10] while Durrington[11] has expressed his doubts on pathophysiological grounds. It is interesting that even Reaven, who first thought about the existence of «metabolic syndrome», has recently admitted that «there is no reason to believe that the metabolic syndrome exists as a distinct clinical entity»[12]**.** Insulin resistance per se does not add any risk to the other risk factors for cardiovascular diseases, which are included in the diagnosis of «metabolic syndrome». In fact the diagnosis of «metabolic syndrome» has not offered any advantage and may be a cause of additional emotional stress to patients[8]. We can admit that the real problem is the sedentary life and obesity of modern societies. I do not deny that diabetes, arterial hypertension and dyslipidemia frequently come together in obese subjects but this coincidence is not a syndrome. Probably the time has come to abandon the perception of «metabolic syndrome» as a syndrome and to focus only on the right treatment of diabetes, obesity, dyslipidemia and hypertension. We can say that, the myth of metabolic syndrome is finally over.

Περίληψη

Καραμήτσος Δ.Θ. **Το μεταβολικό σύνδρομο είναι στην πραγματικότητα ένα τεχνητό σύνδρομο**. *Hellen Diabetol Chron 2006; 3: 171-175.*

Ο Reaven δημοσίευσε πρώτος το 1988 την άποψη ότι η συνύπαρξη διαταραχής στην ανοχή της γλυκόζης, δυσλιπιδαιμίας με αύξηση των VLDL και αρτηριακής υπέρτασης είχαν κοινό παθογενετικό υπόστρωμα την υπερινσουλιναιμία ή/και την αντίσταση στην ινσουλίνη και ονόμασε αυτή τη συνύπαρξη σύνδρομο Χ που αργότερα ονομάστηκε μεταβολικό σύνδρομο. Είναι γενικά αποδεκτό ότι αυτοί οι παράγοντες αυξάνουν την προδιάθεση για αθηρωμάτωση. Η θεωρία του μεταβολικού συνδρόμου απέκτησε γρήγορα υποστηρικτές και στηρίχθηκε οικονομικά από μερικές φαρμακευτικές εταιρίες, οι οποίες – για δικούς τους λόγους – βρήκαν το έδαφος να διαφημίσουν εμμέσως (συνέδρια, έντυπα) προϊόντα τους, τα οποία δεν δρουν μέσω αυξήσεως της έκκρισης ινσουλίνης. Παρά την παρέλευση 17 ετών ο καθορισμός διαγνωστικών κριτηρίων για τη διάγνωση του μεταβολικού συνδρόμου δεν έχει καταλήξει σε ομοφωνία. Επιπλέον τα διαγνωστικά ή φυσιολογικά όρια βιοχημικών και κλινικών παραμέτρων συνεχώς μειώνονται, ώστε γίνεται πιθανό η πλειονότητα του ενήλικα πληθυσμού

να θεωρηθεί ότι πάσχει από μεταβολικό σύνδρομο. Οι ευρύτερα γνωστές ομάδες κριτηρίων είναι αυτές της WHO, της IDF της EGSIR ,της ATP III, οι οποίες ωστόσο διαφέρουν μεταξύ τους και περιλαμβάνουν πολλές παραμέτρους και διαφορετικές μεθόδους διάγνωσης. Με συνδυασμό των παραπάνω παραμέτρων στις μεθόδους καθορισμού της διάγνωσης μπορεί να τεθεί διάγνωση με 11 διαφορετικούς συνδυασμούς στις πρώτες τρεις (WHO, IDF, EGSIR) και 16 συνδυασμούς (με την ομάδα κριτηρίων NCEP ATP III). Ο όρος «αντίσταση στην ινσουλίνη» σε άτομα που έχουν σακχαρώδη διαβήτη σημαίνει αυτομάτως βιολογική έλλειψη ινσουλίνης. Αυτό εξηγείται από το ότι στον σακχαρώδη διαβήτη τύπου 2, εκτός από την αντίσταση στην ινσουλίνη, απαραίτητη προϋπόθεση για την εμφάνιση της νόσου είναι η μειονεκτική έκκριση ινσουλίνης. Επομένως και οι συσχετίσεις της αντίστασης ινσουλίνης (που μετριέται με τη μέθοδο Clamp) με διάφορες παραμέτρους είναι ουσιαστικά συσχετίσεις έλλειψης ινσουλίνης. Η έλλειψη ινσουλίνης –κατά συνέπεια και η αντίσταση στην ινσουλίνη όταν υπάρχει διαβήτης– προκαλεί υπεργλυκαιμία και δυσλειτουργία του ενδοθηλίου με αποτέλεσμα προδιάθεση για αθηρωμάτωση. Η έλλειψη ινσουλίνης σχετίζεται επίσης και με υπερπηκτικότητα. Όσον αφορά στο πολυσυζητούμενο μεταβολικό σύνδρομο, ενισχύεται τελευταία η άποψη ότι πρόκειται για τυχαία συνύπαρξη ορισμένων παραγόντων κινδύνου για καρδιαγγειακή νόσο, που όμως λόγω αλληλεπιδράσεων ενδέχεται να επιδεινώνονται π.χ. η υπεργλυκαιμία και η δυσλιπιδαιμία που συνδέονται σε φαύλο κύκλο. Προς την κατεύθυνση αυτή συνηγορούν και πρόσφατα άρθρα στο Diabetologia. Προσπάθειες να συσχετισθούν οι συγκεντρώσεις ινσουλίνης πλάσματος με τα τελικά σημεία αγγειακής νόσου σε διαβητικά άτομα δεν είχαν σαφή αποτελέσματα. Το αποκαλούμενο μεταβολικό σύνδρομο δεν εξηγείται από ένα κοινό παθογενετικό αίτιο και πιθανώς είναι αποτέλεσμα συνέργειας μεταξύ γενετικών παραγόντων και επιδράσεων περιβαλλοντικών. Είναι ενδιαφέρον ότι ακόμη και ο ίδιος ο Reaven πρόσφατα παραδέχθηκε σε άρθρο του ότι «δεν υπάρχει λόγος να πιστεύουμε ότι το μεταβολικό σύνδρομο υπάρχει ως μια ξεχωριστή κλινική οντότητα». Η ινσουλινοαντίσταση και η διάγνωση μεταβολικού συνδρόμου με οποιαδήποτε κριτήρια δεν προσθέτει επιπλέον κίνδυνο πέραν των συμπαρομαρτούντων παθολογικών καταστάσεων, άρα δεν έχει ως διάγνωση καμία πρακτική σημασία. Οι συνιστώσες του μεταβολικού συνδρόμου απαιτούν έτσι και αλλιώς αντιμετώπιση άσχετα με τη διάγνωση του «συνδρόμου». Η ινσουλίνη δρα με πολλούς μηχανισμούς παρεμποδίζοντας την αθηρωμάτωση και θρόμβωση, είναι επομένως μια κατεξοχήν αντιαθηρωματογόνος ορμόνη γι' αυτό και η αθηρωμάτωση αυξάνεται σε συνθήκες έλλειψής της, όπως όταν υπάρχει σακχαρώδης διαβήτης τύπου 2 (έλλειψη ινσουλίνης και αντίσταση στην ινσουλίνη). Μάλλον ήρθε η ώρα να εγκαταλειφθεί ο όρος μεταβολικό σύνδρομο και να αντιμετωπίζουμε απλά την υπεργλυκαιμία, τη δυσλιπιδαιμία και την αυξημένη αρτηριακή πίεση όπως απαιτείται, χωρίς υπερβολές και αναφορές σε τεχνητά σύνδρομα.

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