Editorial
Understanding the pathogeny of diabetes needs a new paradigm

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I do not know if this very complex syndrome called diabetes mellitus needs a new paradigm. It is however obvious that it needs another perspective. This perspective should start with the definition, go trough the pathology and end with the treatment.

Diabetes mellitus is a syndrome characterized by a severe decrease of beta cell mass/function induced by an over-expression of the apoptotic factors in report to those for beta cell regeneration. There are different phenotypes of diabetes, mostly conditioned by two parameters: **age at onset** and the **speed** of the beta cell mass/function decrease. These two characteristics are also influenced by the **primary cause** of diabetogenesis, which can be defined considering the **genetic background** of every phenotype [1-6].

Pancreatic beta cell has an important role in the energy homeostasis of the human body. This particularity is reflected by the fact that the pancreatic beta cell is controlling the metabolism of carbohydrates, lipids or proteins altogether. The progressive decrease of insulin secretion, as a direct consequence of beta cell mass/quality decrease, leads to an excessive catabolism, directly correlated with the amplitude of the secretion failure. On the contrary, an increase in beta cell secretion induces an excessive anabolism for carbohydrates, lipids or proteins. Every insulin dependent tissue in humans has certain characteristics according to its specific role in the body: the **liver** is a real factory for the nutrients, which are both specifically modified and integrated in an inter-metabolic network; the **adipose tissue** collects the energetic overload available at a certain moment in the system; the **muscle cell** is the main user of energy. This is the reason why any disturbance in the metabolic network between these tissues (in addition to the insulin secretion defect) induces a specific phenotype of diabetes, which has to be characterized from a genetic, molecular and biochemical perspective.

Considering all these general remarks, we should point out that **hyperglycemia**, which has been considered for the last 150 years the most characteristic diabetic disturbance and the main **marker** of this syndrome, has not yet been mentioned. Even though currently this attitude can be considered like ostentatious, I'm convinced that in the very next future the scientific community is going to wonder how this idea has been accepted for such a long time despite the increasing amount of evidence clearly showing that hyperglycemia is only a late **epiphenomenon** of the beta cell failure. It is very well known that the failure of the glycemic homeostasis appears when 50% of the beta cell mass is already destroyed. From this perspective it is obvious that hyperglycemia characterizes only a late and irreversible stage in a progressive pathogenic process which involves an exhaustion of the compensatory mechanisms either from the

pancreas (failure of beta cell regeneration) or all over the body (lipids over-storage in different other non-adipose tissues; disturbances of glycolysis/ glycogenesis/ gluconeogenesis ratio; triglycerides accumulation into the liver; lipids alteration into the blood flow, etc) [6-10].

At this point, I have to make two different remarks. **The first remark** is that every insulin dependent tissue previously mentioned occupies a different position in the biochemical structure of the human body; this is why they have different significations in diabetogenesis. **The muscle** works like a permanent engine and this is the reason why it represents the main energy user in the human body. Increased physical activity will strongly prevent diabetogenesis, especially due to either limitation of adipose over-storage or increase of the adipose tissue insulin sensitivity. The insulin amounts used by a physically active person will be lower and the beta cell will be protected, especially in the presence of any other condition associated with a reduction of the beta cell structure or function. On the contrary, a lack in physical activity progressively leads to an increase of lipid storages in either adipose tissue (which also involves an increase of the beta cell mass) or muscle (which alters different metabolic pathways, especially glucose transport – a condition which defines the real insulin resistance state – or mitochondrion oxidative phosphorilation – a condition which has been by mistake considered as related to insulin resistance) [11].

In this scenario, the muscle can prevent diabetogenesis either in an active manner – by an increase of energy expenditures – or in a passive one, by usage of different nutrients in different conditions associated with a lack of physical activity. From the same perspective, the **adipose tissue** plays a **passive role,** in two convergent manners: both increase of nutrient intake and/or decrease of energy expenditure lead to an increase of calorie storage due to an imbalance between calorie intake and use. This is for sure the main mechanism which explains obesity. Obesity implies also a genetic background which defines the incapacity of the uncoupling proteins to eliminate the calorie overload as heat. The tropism of the lipid storages for the big epiploon (defining the abdominal obesity) or subcutaneous tissue (describing the peripheral obesity) is also related to specific genetic factors which are not yet well known. It is though speculated that an exaggerated capacity of the adipocyte precursors to proliferate to adipocytes is responsible for "hyperplasic obesity", but a decrease of this capacity can generate "hypertrophic obesity". In the future, it is possible that genetic research will change its focus from the study of genes to that of gene related transcriptional factors. Many such transcriptional factors (e.g. the transcriptional factor for insulin gene) have been already described and many of them proved to be the link between genetic predisposing factors and different environment factors. If the nutrients are considered, some fatty acids, amino acids or carbohydrates can play much more important roles in diabetogenesis than previously considered [1, 12].

The second remark refers to the fact that at diabetes onset, the most important feature is represented by the beta cell failure, expressed either by a reduced beta cell mass or function. This aspect is probably the real first cause of

diabetes. One diabetogenic hypothesis could be that an apparently minor beta cell defect, such as a disturbance in the maturation process of insulin secreting vesicles, can lead to an increased content of proinsulin versus insulin in comparison with a normal state [13-16]. If the beta cell workload is not increased by one of the factors already mentioned above, the defect can be compatible with a long normal beta cell function. In this case, it is considered that beta cell is a target for a relatively earlier apoptosis that can be compensated by a proportional increase of the beta cell regeneration rate [7, 17, 18]. Unfortunately, there is a lack of data related to whole beta cell life time duration or demonstrating the existence of a compensatory regeneration rate. Even in a diabetic state, the cumulative incidence of the defect is less than 10% in an 80 years old population. The reason for this low prevalence is a genetically conditioned beta cell mass surplus.

One particular diabetes phenotype is represented by autoimmune type 1 diabetes (T1DM). Even though this form is clinically very spectacular, according to our concept one of the main causes for this disease is still represented by the beta cell dysfunction. However, besides this, we think that a second genetically inherited defect involving the immune system must be present. In other words, T1DM pathogenesis involves a small beta cell defect associated with another one involving the autoimmunity genes [6]. One of the strongest proofs for this concept is the fact that beta cell autoimmunity starts with an attack against proinsulin (in fact, the first antibodies which appears in diabetogenesis are anti-proinsulin antibodies) that is subsequently evolving in a wave-string manner, as new waves of immune aggression against the beta cells, explaining the subsequent appearance of GAD or IA-2A antibodies [6, 19].

The immediate consequence of the autoimmune attack is the onset of an apoptotic process which correlates with the intensity of the initial beta cell defect and the specific autoimmune reaction, also. Different degrees of association between these two components generate different phenotypes of autoimmune T1DM, with onset at different ages: infancy (0-5 years), childhood (6-12 years), adolescence (12-18 years), adulthood (>30 years) and even senescence (>60 years) [6, 18]. Currently, it is very well known that autoimmune T1DM is not limited to the small ages, but is encountered even more frequently after the age of 20 years. In this respect, one of our studies [3,] found that only 12,5% of T1DM subjects had onset of the disease between the ages of 0-14 years.

Most cases of autoimmune type diabetes appear in adulthood and can be mistakenly registered either as LADA or non-autoimmune type 1 diabetes. The false picture of autoimmune T1DM as being a characteristic of early ages is due to the “classical” absence of type 2 diabetes cases in these age groups (<10 years). However, we have to point out that this was the reality 20 or 30 years ago. Nowadays, type 2 diabetes is a major health problem in childhood [20], its cumulative incidence increasing even faster than that of type 1 diabetes. In a few decades, it is expected that a reversed pattern of incidence for T1DM/T2DM in children and adolescents will be present, especially if special measures will not be dedicated to stop the natural

increasing tendency of obesity and T2DM in these age groups.

A reduction of the beta cell mass is the fundamental pathogenic mechanism for type 2 diabetes mellitus, also. The difference from the T1DM phenotype is the lack of autoimmunity, the speed of apoptosis – much lower in type 2 phenotype –, and the increased beta cell regeneration rate – apparently even higher than in T1DM. Compared with T1DM, in type 2 diabetes the pathogenic mechanisms appear to be much more numerous. In most cases, the amyloid transformation of amylin (which is co-secreted with insulin during the exocytosis of insulin-containing vesicles) seems to be much more important than previously considered [22-25]. The beta cell toxicity of the amylin oligomers is now very well documented and the mechanism responsible for the amyloid transformation of amylin was identified [25-28]. The primary cause of the defects involving proinsulin and amylin processing needs to be explored at organelles level, especially in the Endoplasmic Reticulum (ER) and Golgi Apparatus (GA). These structures are the main players in the process of generation of the insulin secreting vesicles and incorporation of different partially processed molecules in the already formed vesicles [28, 30-32]. In our opinion, this subcellular compartment is the place where the beta cell primary defect needs to be sought. This initial ER/GA defect is somehow transferred to the insulin-containing vesicles, and finally becomes apparent in the form of several characteristics: increase of plasma proinsulin levels, decrease of mature insulin secretion, generation of amylin oligomers, amyloid transformation of amylin and extracellular amyloid accumulation in the islets. Diabetes onset is finally the result of an increased beta cells apoptosis with a progressive decrease of the beta cellular mass. These events take place very early in the natural history of diabetes, in fact many years before the onset of hyperglycemia. All this evidence strongly suggests that hyperglycemia needs not to be considered anymore as the unique marker for diabetes. More appropriately, hyperglycemia should be maintained as a marker for the late and irreversible stage of diabetes.

The main conclusion for this very succinct review of diabetes pathogenesis is that the common link between all diabetic phenotypes is represented by the beta cell failure, expressed as a progressive reduction of the beta cell mass and/or function. In the very early stages, this process involves discrete hormonal and biochemical disturbances, which have been identified in studies conducted on offspring of type 2 diabetes patients or homozygote twins with and without diabetes.

Hyperglycemia is another common feature for all diabetic phenotypes, but it reflects only a late and irreversible phase of diabetogenesis. This is the reason why the disease needs to be urgently re-defined, and a new early marker for beta cell dysfunction along with new noninvasive methods to evaluate the pancreatic beta cell mass need to be identified. In this aspect, detection of at least one extracellular marker for beta cell apoptosis looks extremely useful, even though currently none was identified.

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