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Editorial

MEDICINE SHOULDN'T BE CONSIDERED A GOOD BUSINESS

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Pharmaceutical industry is an important piece in diabetes care as long as it doesn't have as its main purpose only to be a very profitable industry. When this happens, the risks are high for patients, but also for those who produce some drugs which, after 10 years of clinical use, must be withdrawn from the market due to serious adverse effects.

The Glitazones (Thiazolidinediones, TZDs) class started with troglitazone, a drug which was rapidly withdrawn from clinical use due to its frequent side effect of severe liver damage [1]. The next two members of this class, rosiglitazone and pioglitazone have been approved in 1999 for the treatment of hyperglycemia in type 2 diabetes (T2DM). These drugs slightly reduced blood glucose, leading to a HbA1c reduction of ~1 %. However, they were subject of intense media coverage due to some putative positive effects such as uptake of free fatty acids (FFA) from circulation and their deposition in adipocytes, leading to an improvement of peripheral insulin resistance. In addition, producers and supporters advocated the use of TZD's inducing the idea of a possible effect of β-cell mass increase, an effect identified in some animal models but never confirmed in humans [2].

From the beginning however it has been noted that these drugs are associated with an increase in body weight (sometimes significant, above 10 kg in two years), some adverse effects on the lipid profile, fluid retention, and anemia [3]. The adverse effects on the lipid profile were more significant for rosiglitazone, increasing the potential for adverse cardiovascular (CV) outcomes in patients treated with this drug. This "*hypothetical scare*" became a sad reality in 2007 when the first strong proof was published regarding the increased risk for myocardial infarction and death in diabetic patients treated with rosiglitazone [4,5]. A few years followed during which the advocates of TZDs tried to sweeten the reality of increased CV risk.

Retrospectively, a clear and strong link between the orientation of authors' expressed views on the rosiglitazone controversy and their financial conflicts of interest with pharmaceutical companies was established [6]. Fortunately, the efforts of the pharmaceutical industry to protect its „*guilty child*" failed and in September 2010 the

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European Medicine Agency (EMA) decided to suspend the market authorization of rosiglitazone in Europe, while the Food and Drug Administration (FDA) decided to restrict the use of rosiglitazone in USA. The end of the story for rosiglitazone came this year when on the second of July, the US Department of Justice announced that GlaxoSmithKline (market authorization holder of rosiglitazone) agreed to plead guilty to three criminal counts and settle civil charges of $3 billion to the federal government and participating states [7].

Another setback of the TZDs was the increased risk for bone mass loss, osteoporosis and increased risk of fractures. The data were evident in animal models [8] and reported in humans as early as 2006 [9]. More and more studies followed confirming the initial reports [10,11]. In a very recent analysis of a nationwide database of prescriptions in Scotland [12] it was concluded that hip fracture is a serious adverse effect of TZDs, affecting both sexes, needing that labels should be changed to warn of this.

Finally, the curtain dropped on the TZD class following the confirmed reports of increased risk of bladder cancer in pioglitazone treated subjects [13,14]. This led to official recommendations from both the FDA in USA and EMA in Europe. Thus, FDA recommended inclusion of the information regarding the increased risk of bladder cancer to the *Warnings and Precautions* section of the label for pioglitazone-containing medicines [15]. In the same time, EMA asked the prescribers to *"carefully select patients and monitor response to treatment"* and the marketing authorization holder to "*conduct a pan-European epidemiological study focusing on more robust characterization of the risk*" [16].

Following all these negative reports regarding the effects of TZDs, already in 2009 Scheen et al. in a *Diabetologia* editorial referring to rosiglitazone raised the question "*To be or not to be?*" [17]. Two years later, a commentary on this topic was published in JAMA by Lipska and Ross [18]. Their editorial ends with a wise thought: "*It is time to think outside this class*".

However, I think this discussion should focus mainly on the causes that led to the "*evil*" of TZDs, a phenomenon to which medical research is not a stranger. At the end of the 90s, I was myself an enthusiast of the above mentioned class. The launch of the TZD class has been preceded, accompanied and followed by an impressive number of papers. From the period of TZD's class launch, I remember entering the huge Poster Hall in the evening, at the end of an American Diabetes Association (ADA) meeting congress day. I've been impressed by 15, maybe 20 stocks of reprints distributed from place to place, below the posters, as I've never seen before. Curious, I looked at the first, then the second, and then the fifteenth. All were reporting TZD's studies results. All were printed on high quality A3 paper with professional prepared graphic presentations. All had conclusions indicating solid proof regarding the *insulin sensitizer* efficacy in reducing insulin resistance.

At the end of the last century, the "*hypothetical*" peripheral insulin resistance concept has already been presented as the primary cause of T2DM, metabolic syndrome, non-alcoholic fatty liver or other metabolic disorders. Without denying the existence of

peripheral insulin resistance, this disturbance cannot be *primary* but only *secondary* to other derangements which, in our view, are often induced by overweight/obesity. In contrast with the hypothetical concept of peripheral insulin resistance, obesity is a very harsh and concrete reality. This is a reality we observe daily in our offices; we see it on the street and on TV. Obviously, researchers are not to blame for the actual epidemic of diabetes and obesity. However, some included in the concluding remarks of their articles devoted to the "*Fata Morgana*" of insulin resistance the suggestion of the urgent need for the identification of "new molecular targets" for this "illusion".

Among these targets, the peroxisome proliferator activated receptors gamma (PPARγ) enjoyed a special attention because they are indeed involved in many biochemical processes operating in many cells/tissues/ organs. In hundreds of studies dedicated to the putative mechanisms of insulin resistance, it has been found that the agonists of PPARγ are able to increase the sensitivity to insulin. Unfortunately this effect is induced by stimulation of adipogenesis, a phenomenon that explains the weight gain during the treatment with TZDs, often associated with a deterioration of lipid profile and subsequent increase of cardiovascular risk. This is due to the fact that TZDs can not influence specifically only mechanisms with positive effects, like fatty acid oxidation in liver and skeletal muscles. In the same time they activate mechanisms with negative consequences such as adipogenesis and increase in body weight. In the short term, TZDs can decrease blood glucose and "clear" fatty acids from the circulation, with the consequence of increased fatty depot in adipocytes. On the long term, deterioration of the lipid profile appears (at least for rosiglitazone) leading to an increase in the cardiovascular risk.

The concept of insulin resistance considered to be *per se* the "primary cause" of this disorder was clearly demonstrated to be erroneous. We can accept the existence of several biochemical alterations associated with a decrease in some of the peripheral actions of insulin, generally related to the effect of some proinflammatory cytokines interfering with the metabolic pathways in various tissues. However, such derangements are not *primary*, but *secondary* alterations, direct consequence of obesity via lipotoxicity and oxidative stress. That fact that common insulin resistance is a secondary phenomenon is clearly proved by the results of bariatric surgery: a decrease in body weight will rapidly lead to the disappearance of the putative insulin resistance [19].

In our view, the relationship between insulin resistance and obesity can be compared to the *body and its shadow* [20-22]. When the body (in this case obesity) stands in sunlight, the shadow (in this case insulin resistance) will of course appear. If our therapeutic gun is targeting *the shadow* (insulin resistance), the PPARγ bullet will not harm *the shadow*, but for sure various tissues might be injured. In our view, the insulin resistance term must be reanalyzed in order to avoid the confusion existing today, when it is used in order to explain a large array of conditions, sometimes as a hypothetical pathogenic mechanism or as a part of the conceptual interpretation of some metabolic disturbances. We think that the term of *insulin resistance* is like an over inflated

balloon on the verge of bursting. It requires clarification in order to separate reality from fiction [22].

From Hippocrates to date, it was often repeated that prevention is better than cure. Unfortunately, the modern "*consumer based*" types of society which influence the appearance of the metabolic pathology is not dependent on the medical specialists [21]. As a passer-by through the purgatory of the communist society, I am now observing how the hyper-efficient economic model of Western civilization leads to the "explosion" of the number of new cases of diabetes, clearly evidenced by the dynamics of new cases recorded in Romania between 1942 and 2011. What will our grandchildren think of us and our scientific research ? Can our present-day politicians think outside this socio-economic model ?

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