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Reply to the letter to the editor entitled: ''Glucocentricity or adipocentricity: The unceasing search for El Dorado''☆

Respuesta a Carta al Editor. «Glucocentrismo o adipocentrismo: la incesante búsqueda de El Dorado»

Sir,

I sincerely thank Dr. Giménez-Pérez for his comments, which undoubtedly contribute to enriching the debate about the therapeutic approach to type 2 diabetes mellitus (T2DM).

Dr. Giménez-Pérez criticizes the choice of body mass index (BMI) and waist circumference (WC) as therapeutic decision parameters, arguing that ''a substantial number of patients with T2DM have normal weight'', a statement supported in his view by data from the UKPDS.[1] However, the UKPDS was not an epidemiological, but an interventional study, and is therefore inadequate for drawing valid data on obesity prevalence in diabetics. As discussed in my article, data from the NHANES study[2] show that 80.3% of patients with T2DM have a BMI greater than 25 kg/m^2 and 49.1% BMI values higher than 30. These figures are similar to those reported in the Spanish Di@bet.es study,[3] where 50.2% of patients with known T2DM and 60.2% of those with unknown T2DM had BMI values higher than 30. Although BMI and WC underestimate the pathological increase in abdominal fat, they currently represent the simplest tool for diagnosis of central obesity, and the data provided confirm that most patients with T2DM have increased BMI and/or WC. Based on my adipocentric view of the disease, I cannot share the statement of Dr. Giménez-Pérez that BMI is a subordinate variable in T2DM, and it is obvious that this discrepancy is an essential part of the debate.

On the other hand, Dr. Giménez-Pérez thinks that it is erroneous to state that patients with T2DM and normal weight probably have other forms of diabetes mellitus (DM), as this would represent exclusion from the therapeutic algorithm of T2DM of a substantial number of patients who actually suffer from the disease. However, the data reported show that T2DM is a heterogeneous disease in terms of pathogenesis, causative genetic factors, and clinical characteristics, particularly in patients with lower BMI, and we are thus actually speaking of a group of different disorders having hypoglycemia as a common denominator.[4] For example, 5% of patients diagnosed with T2DM have a form of monogenic diabetes,[4] and in the UKPDS study, 12% of patients with T2DM had GAD65 y and/or IA-2 autoantibodies.[5] This patient subgroup with autoimmune DM had, as compared to the rest of the UKPDS cohorte, lower BMI, modest insulin resistance, low C peptide levels, and no family history of DM, and responded better to insulin therapy as compared to sulfonylureas or metformin. Actually, what is surprising is that uniform therapeutic recommendations are maintained for all patients diagnosed with T2DM (the ''one size fits all'' approach), despite the fact that the heterogeneity of the disease and of the response to the different treatments is all too well known. The algorithm proposed in my article, far from ignoring this fact, makes special mention of the need to explore its etiology in patients with T2DM who are not overweight, as this may lead to a better treatment approach (sulfonylureas in MODY 1 and 3, insulin in LADA, etc.).

The letter mentions the lack of data on morbidity and mortality data in randomized clinical trials, and the questionable relations between weight and complications in patients with T2DM. Pending completion of the Look-AHEAD study,[6] which may possibly answer these two questions, the data reported make it possible to state that in diabetic patients, weight loss achieved through lifestyle changes, drugs and/or surgery simultaneously improves all cardiovascular risk factors, including hypoglycemia. Bariatric surgery has been shown to rapidly resolve T2DM in a large proportion of patients and to decrease diabetes-specific mortality. The studies cited by Dr. Giménez-Pérez concerning the so-called ''obesity paradox'' (lower morbidity and mortality in

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diabetic patients with cardiovascular disease and obesity as compared to patients with normal weight and a potential harmful effect of weight loss) are not free from the significant bias imposed by involuntary weight loss induced by severe heart disease. Randomized clinical trials to assess the effect of involuntary weight loss on total and cardiovascular morbidity and mortality in this patient group are needed.

Dr. Giménez-Pérez expresses his concern for ''a change in priority from treatment for hypertension and dyslipidemia to treatment for excess weight''. Nothing was further from my mind: I emphasize in my article that antihypertensive and lipid-lowering drugs have synergistic effects with weight loss for decreasing cardiovascular risk. However, if we are able to reduce patient weight, the number and dose of these drugs may probably be decreased, as seen in the first four years of the Look-AHEAD study.[6]

The remark about metformin and its effect on microvascular complications in T2DM is completely relevant. In UKPDS, metformin achieved in overweight patients a significant reduction in total and DM-specific mortality, clinical events related to DM (a composite endpoint also including microvascular complications), and myocardial infarction, but secondary analysis of microvascular complications alone showed no statistical significance with metformin, insulin, or sulfonylureas.[7] The metformin group showed a marginally significant lower progression of retinopathy at nine years. The risk reduction seen with metformin for microvascular complications (RR 0.71) was of a magnitude similar to that reported for insulin and sulfonylureas in the UKPDS, which was not restricted to overweight patients, but was in the latter case statistically significant.[1]

Finally, the letter criticizes the recommendation of drugs for which there has been little experience of their use for second-line treatment. It should be noted that the glucocentric algorithms published include from the second therapeutic step recommendations that are not supported by any clinical trial, but are based on expert opinions. In the UKPDS study, an unexpected increase occurred in mortality related to DM with the combination of metformin and sulfonylurea, a finding that has not yet been adequately clarified. This is therefore a field of great scientific uncertainty open to criticism and discussion. The three drug classes I recommend (metformin, GLP-1 receptor agonists, and orlistat) induce simultaneous improvement in several cardiovascular risk factors, a pleiotropic effect not shared by other conventional alternative treatments. Ongoing clinical trials, such as the LEADER study with liraglutide or the EXSCEL study with exenatide LAR, will try and ascertain whether these beneficial changes in multiple factors will result in a long-term reduction of cardiovascular risk.

I share with Dr. Giménez-Pérez his concern about the safety and long-term results of metabolic surgery, and I think that this is clearly explained in the article.

El Dorado was a myth fuelled by the greed of unscrupulous individuals which caused many deaths over years of unsuccessful searching. In this debate, I obviously prefer another parallelism, semantically closer, to the controversy which arose centuries ago between geocentrism and heliocentrism. On reflection, however, considering what happened to Galileo, I would be well-advised to avoid historical analogies...

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