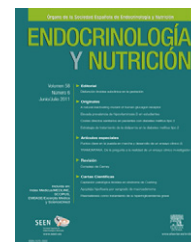




# ENDOCRINOLOGÍA Y NUTRICIÓN

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## LETTERS TO THE EDITOR

### Glucocentricity or adipocentricity: The unceasing quest for El Dorado<sup>☆</sup>

#### Glucocentrismo o adipocentrismo: la incesante búsqueda de El Dorado

I have read with great interest the reflections of Gorgojo Martínez<sup>1</sup> about the best therapeutic approach to patients with type 2 diabetes mellitus (T2DM) and his decision to place his bet on focusing attention on excess weight management to the detriment of treatment focused on blood glucose control. I must admit that this is an attractive idea that will undoubtedly have many supporters, of which I may become one, after an appropriate discussion. There are however some aspects in his approach that I would like to qualify.

First of all, when defining the adipocentric approach, the author states that the main parameters in T2DM should be body mass index (BMI) and waist circumference (WC). It is obvious that for a variable associated with a disease to be considered as a main parameter, i.e. the therapeutic target, it should be altered in all individuals with the disease. While the relationship between and T2DM is true and evident, it is not less true that a substantial number of patients with T2DM have normal weight. As an example, in the UKPDS<sup>2</sup> study, initial BMI in the study population was 27.5 kg/m<sup>2</sup> with a standard deviation of 5.2 kg/m<sup>2</sup>, which, assuming a normal distribution of the population, means that approximately 16% of patients had an initial BMI less than 22 kg/m<sup>2</sup>. The author tries to explain this circumstantial oblivion regarding a not negligible number of patients by stating that patients with "T2DM and normal weight probably have other forms of DM such as LADA or monogenic or secondary DM". However, this statement is far from true. Even assuming that other forms of DM are more common in patients with normal weight, no sufficient data are available in the literature to state that all, or even a majority, of adult patients with DM and normal weight have a disease pathogenetically different from type 2 diabetes.<sup>3</sup> Thus, if we use BMI or WC as a main parameter, we run the risk of not including in the therapeutic algorithm of T2DM a substantial number of patients who actually suffer the disease.

Second, we should not forget that the true objective in treatment of T2DM is to improve the quality and life expectancy of patients. It is clear that glucocentric approaches have shown great limitations regarding the achievement of this goal. However, the same is similarly or even more true of the adipocentric approach, as is shown by the lack of data on morbidity and mortality variables from randomized clinical trials and the questionable relations between weight and complications in patients with T2DM.<sup>4,5</sup> In my opinion, it is clear that the most robust current strategy is a multifactorial approach.<sup>6</sup> In this regard, prioritization of excess weight management over treatment of hypertension and dyslipidemia ("... but we may probably avoid the use of multiple drugs if the patient achieves weight goals") is worrying.

The author's statement about the beneficial effect of metformin treatment on microvascular complications in the UKPDS study deserves a separate comment. Although this was not the main study endpoint, the truth is that neither in the initial study<sup>7</sup> nor in the follow-up study<sup>8</sup> did the group randomized to metformin show any significant differences from the conventional group regarding the microvascular complication rate.

The author's approach contains other debatable aspects which I will only indicate briefly for reasons of space, such as advocating the use of novel drugs as a second line treatment before their significant effects on robust variables and clearly proven long-term safety have been shown, or the uncertainty about the long-term persistence of the benefits of metabolic surgery in the absence of morbid obesity.

To sum up, this is a daring and welcome approach, but one that runs the risks of leaving behind a substantial number of patients with T2DM, of playing down the achievement of blood pressure and lipid goals by focusing too much on weight goals, and of prioritizing a subordinate variable without having adequate evidence of the benefits of such a strategy. For the time being, I myself will not be searching for El Dorado and will continue to make do with a prudent but safer approach.

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## Reply to the letter to the editor entitled: "Glucocentricity or adipocentricity: The unceasing search for El Dorado"<sup>☆</sup>

### 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.<sup>1</sup> 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<sup>2</sup> show that 80.3% of patients with T2DM have a BMI greater than 25 kg/m<sup>2</sup> and 49.1% BMI values higher than 30. These figures are similar to those reported in the Spanish Di@bet.es study,<sup>3</sup> 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.<sup>4</sup> For example, 5% of patients diagnosed with T2DM have a form of monogenic diabetes,<sup>4</sup> and in the UKPDS study, 12% of patients with T2DM had GAD65 y and/or IA-2 autoantibodies.<sup>5</sup> This patient subgroup with autoimmune DM had, as compared to the rest of the UKPDS cohort, 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,<sup>6</sup> 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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