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Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 23192

Manuscript Type: REVIEW

Answering reviewers

► Reviewer 1

1. In Tables 1 and 2, it may add some major references.

Response

I added some references in Table 1. Table 2 and Table 3 were deleted because the evidence was equivocal in some descriptions.

2. In Figure 1, the source of citation is lacking. The citation should be clearly indicated in the figure legend.

Response

The corresponding citation was indicated.

3. In Figure 2, there is only a figure level "a", but where is "b" or others? Please check the number of presented figure. Moreover, the citation should be clearly

indicated in the figure legend.

Response

A figure level "a" was deleted. The corresponding citation was indicated.

► Reviewer 2

Is there any link between low levels of serum amylase and NAFLD?

Response

The new reference "World J Gastroenterol. 2013 Jun 14;19(22):3375-84.", which suggests a link between low metabolic syndrome and NAFLD, was added as a reference (no. 39).

► Reviewer 3

None

► Reviewer 4

1. The review has an interesting topic, but the message of the "novel" interpretation seems to be lacking. The message of the "novel" interpretation be clearer and in the presented as the main message.

Response

I agree with this comments.

Then, to improve the message, next sentences was added in the paragraph of “Novel interpretation”

“Except for these early studies [35-37], no clinical studies have investigated the relationship between serum amylase and obesity and obesity related conditions.”

“Furthermore, in our previous study of asymptomatic subjects who were not being treated for diabetes [44], homeostasis model assessment of insulin resistant, plasma insulin level at fasting and at 60 min in the 75g oral glucose tolerance test were significantly associated with low serum amylase (<60 IU/l) after adjustment for relevant confounding factors including BMI, although the sample size was small (n = 54).”

This indicates the relationship between low serum amylase and insulin resistance.

“Obesity, as a condition associated with various cardiometabolic diseases concomitant with insulin resistance, may be a major determinant for low serum amylase in the general population (a novel interpretation).”

2. There seems to be several changes in font and some grammatical issues throughout the manuscript. Please proofread to correct these issues. Abstract:

1. Page 2: line 5: The sentence “Because insulin-dependent diabetes is less prevalent....in a general population” is confusing. Please restate the thought.

Suggest possibly separate into two sentences.

Response

I agree with this comments.

The sentences was changed into the following.

“In the most populations, insulin-dependent diabetes is less prevalent (minor contribution) compared with insulin-independent diabetes, and obesity is highly prevalent compared with low body weight. Therefore, obesity, as a condition that elicits cardiometabolic diseases relating to insulin resistance”

2. Page 2: line 7: “and obesity is highly prevalent, obesity, as a condition...” The use of the term obesity twice in this sentence is confusing. Please correct, so proper interpretation is delivered.

Response

I agree with this comments.

The sentences was changed into the following.

As in the above, the sentences was changed into the following.

“In the most populations, insulin-dependent diabetes is less prevalent (minor contribution) compared with insulin-independent diabetes, and obesity is highly prevalent compared with low body weight. Therefore, obesity, as a condition that elicits cardiometabolic diseases relating to insulin resistance”

3 Introduction: 1. Page 3: Para 1: The authors use “(EC 3.2.1.1)” in the first sentence. Please indicate what this term means.

Response

The term “(EC 3.2.1.1)” was deleted because of misleading.

4 Novel Interpretation: 1. Page 8: Para 1: The first three lines seems to have different spacing than the majority of the manuscript. Please format correctly. There are several other times throughout this manuscript that have similar formatting irregularities. Please proofread to correct as I will not comment on these anymore. Other conditions affecting amylase levels: 1. Page 11: Para 2: “Meanwhile, some clinical studies have shown...” changes font within the sentence. Please format correctly.

Response

Space and font were fixed throughout the text.

Page 12: Para 1: The authors state “Together with lower prevalence ofindicates that” Not only is this statement is incomplete, but the entire section is incomplete. This section needs to be completed, so the thoughts trying to be portrayed in this manuscript can be properly interpreted.

Response

I agree with this comments. The sentences were added to complete the section as follows.

“Together with putative lower prevalence of pancreatic cancers in individuals

with O blood type [80-82] indicates that there might be a certain relationship between ABO blood type, which is under strict genetic regulation, and the susceptibility of pancreatic disease. ”

Tables: 1. Are there any statistics to confirm these relationships? Even though these are listed as plausible, one would assume that these plausible relationships were based off some form of data. Inclusion of this data would greatly help.

Response

I added some references in Table 1. Table 2 and Table 3 were deleted because the evidence was equivocal in some descriptions.

► Besides response to the comments of reviewers, I added some sentences highlighted with red to improve the manuscript.

Page 8

Williams et al.[46] mentioned in an early review article that insulin is necessary for normal acinar function and that endogenous insulin potentiates zymogen release. However, exogenous insulin supplementation can improve low serum amylase in type 1 diabetes[13]. Schneeman et al.[35] proposed in an animal study that insulin resistance may prevent the potentiating effect of insulin on amylase synthesis, leading to lower amylase levels. Early clinical studies have

also shown that serum pancreatic amylase was closely related to C-peptide concentration and pancreatic β -cell function[13,14].

Page 8

We experienced a similar result in an entirely different Japanese population (unpublished data). These findings may be consistent with the results of an early study by Dandona et al.[14], which showed no significant correlation between HbA1c and pancreatic amylase activity.

Page 11

This may occur via damage of pancreatic tissue, i.e., chronic pancreatitis, and reduced salivary amylase[66]. However, the underlying mechanism may be complicated because the effect of alcohol on glucose homeostasis can differ according the quantity consumed[67], age, and lifestyle[68].

Page 13

lower amylase can be converted to normal amylase as a result of diminished clearance. GFR, for instance by the use of insulin, is not measured in usual clinical settings, so eGFR should be at least considered as a relevant confounding factor in the analysis of serum amylase. Nevertheless, it is unknown whether hyperfiltration, which is often observed in early diabetes, lowers serum amylase.

Thirteen references were added (highlighted with red) in the revised manuscript.

