

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**ESPS manuscript NO:** 22232

**Title:** Osteocalcin as a hormone regulating glucose metabolism

**Reviewer's code:** 00203715

**Reviewer's country:** Germany

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2015-08-24 08:30

**Date reviewed:** 2015-09-04 21:19

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> [ Y] Accept
<input type="checkbox"/> [ Y] Grade B: Very good	<input type="checkbox"/> [ Y] Grade B: Minor language polishing	<input type="checkbox"/> [ ] The same title	<input type="checkbox"/> [ ] High priority for publication
<input type="checkbox"/> [ ] Grade C: Good	<input type="checkbox"/> [ ] Grade C: A great deal of language polishing	<input type="checkbox"/> [ ] Duplicate publication	<input type="checkbox"/> [ ] Rejection
<input type="checkbox"/> [ ] Grade D: Fair	<input type="checkbox"/> [ ] Grade D: Rejected	<input type="checkbox"/> [ Y] No	<input type="checkbox"/> [ ] Minor revision
<input type="checkbox"/> [ ] Grade E: Poor		BPG Search:	<input type="checkbox"/> [ ] Major revision
		<input type="checkbox"/> [ ] The same title	
		<input type="checkbox"/> [ ] Duplicate publication	
		<input type="checkbox"/> [ ] Plagiarism	
		<input type="checkbox"/> [ Y] No	

## COMMENTS TO AUTHORS

The manuscript by Ippea Kanazawa "Osteocalcin as a hormone regulating glucose metabolism" summarizes relevant studies in regards to glucose metabolism and endocrine regulation between bone, fat, pancreas, and muscle. On top of data initiated in the Karsenty laboratory showing that bone is an endocrine organ studies from humans are included. The review is up to date and well written.

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**ESPS manuscript NO:** 22232

**Title:** Osteocalcin as a hormone regulating glucose metabolism

**Reviewer's code:** 02446208

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2015-08-24 08:30

**Date reviewed:** 2015-09-30 03:35

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

This manuscript provides an overview on Osteocalcin and its functions in glucose metabolism as well as their implications in diabetes and obesity. In general, the manuscript was well and concisely written, different aspects of osteocalcin were covered, described and explained with references and logical flow. It is a topic of current biological and biomedical significance with potential impacts in the field of glucose metabolism and diabetes research and future diabetes treatment. However, the relative scarcity of the human data dampens this reviewer's enthusiasm for the protein and for the manuscript. In addition, there are some major and minor concerns associated with the current version of the manuscript. Modifications and updates should be made before the manuscript can be accepted for publications.

1. Major concerns.

1-1. This is a review article. However, only 60 references were listed. This indicates either the narrowness of the field or the scarcity of the research on this topic, which may impact the readership. Author may consider additional references if they are available, particularly those in the recent 10 years.

1-2. This is a review on osteocalcin and its functions or potential functions in glucose metabolism. However, in the Conclusion of the manuscript, the word osteocalcin was not even mentioned. This is both surprising

and puzzling. The word of osteocalcin should be added to the Conclusion, which should be rewritten. 1-3. Positive feedforward loop was mentioned in the Abstract. However, this point was not sufficiently emphasized in other parts of the manuscript including figures. A little more on the loop should be added in the text (particularly the section of "An endocrine loop between bond and pancreas) and/or figures. In the section of "The cross relationships .....", on page 9, lines 10 and 11, "negative feedback loops" were suggested. The relationship between the potential positive loop and this negative loop, if there is any, should be described and discussed. 1-4. According to the author, osteocalcin is apparently anti-diabetic. This reviewer is wondering the reason that not much has been done with this important protein in human and its potential use in treating diabetes. The side effects or potential side effects of the protein should also be covered. In addition, potential technical obstacles, if there are any, in human studies should also be discussed. 1-5. Figure legends may include potential positive or negative loop descriptions. If these loops are inconclusive, dotted lines can be used. 2. Minor concerns 2-1. On page 4, line 34, "and can't" should be "and can not". 2-2. Page 6, line 32, the abbreviation "BMD" should be spelled out if it is mentioned first time. 2-3. Page 7, line 13, the word "resistant" should be changed to "resistance". 2-4. Page 13, line 9, "serum total osteocalcin" should be "total serum osteocalcin". 2-5. Some of the papers used for resistin may be too old. Newer papers should be used. 2-6. Figures should be cited in the text. The inserted figures might not have placed in the most appropriate sites in the manuscript. In addition, without referring to the figures in the text, it is very difficult for readers to go back and forth for the contents covered in the figures.

## ESPS PEER-REVIEW REPORT

**Name of journal:** World Journal of Diabetes

**ESPS manuscript NO:** 22232

**Title:** Osteocalcin as a hormone regulating glucose metabolism

**Reviewer's code:** 03257885

**Reviewer's country:** Italy

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2015-08-24 08:30

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

## COMMENTS TO AUTHORS

Overall this is a nice review of the actual evidence from basic science about the role of osteocalcin as a putative regulator of glucose metabolism. The topic is actual and of interest. The author reviewed many pathways involved in the role of osteocalcin in the regulation of glucose metabolism. However, it seems that the revision of the literature was not very accurate for all pathways. Indeed, as outlined below, for some pathways the author report just one side of current evidence and contrasting evidence have not been discussed. I would appreciate a more balanced review of the literature and a fairly discussion about unsolved controversies. Moreover, I would appreciate if the author can extend the section about human studies. Major revisions

1. Cover Tip. The last cover tip suggested by the author is: "Osteocalcin may be a novel candidate for treatment of type 2 diabetes". In my opinion, to date there is no enough evidence to support this cutting-edge position. Even though the author nicely report what is currently known about role of osteocalcin in the regulation of glucose metabolism, most of the data reported in this review are from preclinical models and few human data have been reported. Thus, I would suggest the author to balance this statement.
2. The author should add the criteria he used for the revision of the literature (database

searched, words used, timespan) and for the decision to include or exclude studies. 3. Page 5, lines 27-28. Mizokami et al showed that exendin, a GLP1 receptor antagonist, blocked the effects of osteocalcin on glucose metabolism and insulin secretion, but they did not show an effect of exendin on the osteocalcin dependent increase of serum GLP1. This sentence could be confusing for readers and thus I would be more precise. 4. Page 6 lines 7-9. Here the author reports data suggesting that uOC do not affect insulin sensitivity. However, there is also evidence showing that osteocalcin is able to increase insulin sensitivity. I would suggest writing about these data too, in order to give reader a more balanced evaluation of the actual knowledge in the field. How does the author explain these contrasting findings? 5. Page 6 line 24 and page 7 line 4. Reference 18 is not correct. Please add the right reference. 6. Page 6 22-24. Here the author writes that "Ferron et al. previously showed that decreased expression of FoxO1 [...] was associated with the glucose intolerance of Ob\_IR-/- mice." However Ferron et al showed that FoxO1 haploinsufficiency (decreased expression of FoxO1) rescued the Ob\_IR-/- phenotype ameliorating the glucose intolerance associated with Ob\_IR-/. This is consistent with the inhibitory effects of insulin on FoxO1. Please check and correct the statement. Thank you. 7. Page 6 line 28-29. There is evidence showing that the interaction between FoxO1 and ATF4 increases osteocalcin inactivation (Kode A et al. J Biol Chem 2012). This seems to be in contrast with the data reported by Rached MT in Cell Metab 2010 that have been discussed by the author. Could please the author critically evaluate, report and discuss these contrasting data? If insulin has an anabolic effect on bones, it is expected that FoxO1 knockout causes an increase in bone mass, but this is not the case of the data reported by the author. How does the author explain this? Moreover, since many WJD readers are clinicians, I would suggest to better explain the insulin/FoxO1/ATF4 pathway not assuming that the readers have a deep knowledge of this pathway. In particular, it is not clear if the author suggests that insulin has anabolic effects by inhibiting FoxO1 or not. 8. Page 9 Lines 21-27. The author writes that his own data (ref 41) are in contrast with those published by Luo (Ref 40). However, to the reviewer's understanding, this is not the case. Lou et al. showed that adiponectin increases ALP activity and osteocalcin expression in human osteoblasts. As well, Kanazawa's pap