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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 11492

Title: Increased circulating zonulin in children and adolescents with biopsy-proven nonalcoholic fatty liver disease

Reviewer code: 00038192

Science editor: Su-Xin Gou

Date sent for review: 2014-05-26 14:05

Date reviewed: 2014-05-26 15:55

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

COMMENTS TO AUTHORS

Please explain abbreviations in the abstract. Please correct the few spelling and grammatical errors like page 5, gardians; page 11 paients. Table 1, Fasting glucose and 2 h glucose should be given in same units. Figure 2, please show graphs for distribution of zonulin in relation to inflammation and fibrosis.



ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 11492

Title: Increased circulating zonulin in children and adolescents with biopsy-proven nonalcoholic fatty liver disease

Reviewer code: 00053423

Science editor: Su-Xin Gou

Date sent for review: 2014-05-26 14:05

Date reviewed: 2014-06-03 04:49

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

The study of Pacifico et al investigated the relation between zonulin, a marker of intestinal permeability, and stages of hepatic disease in obese children with biopsy confirmed NAFLD. They observed correlation between zonulin and steatosis severity but no correlation with inflammation, ballooning, fibrosis score and NASH diagnosis. They suggested that their findings add data to the hypothesis that simple steatosis and NASH are different, not necessarily inter-related diseases.

Comments Subjects of the study with NAFLD had BMI-SD score (2.15(0.50) vs. 2.10(0.32)) and subcutaneous adipose tissues (1828 vs.1648) apparently greater than without NAFLD. The authors should include p-value of comparisons. Patients with NAFLD had visceral adipose tissue significantly higher than those without NAFLD. Also, subjects with NAFLD had most glucose metabolism parameters evaluated higher than those subjects without NAFLD, and lower WBISI values compared to subjects without NAFLD. Considering obesity and glucose intolerance are potential confounding variables, the correlation analysis for variables associated with zonulin should be further adjusted for adipose tissue parameters and glucose metabolism parameters, besides age, gender and puberal status. Quite unexpected, no relation was found between zonulin concentrations and BMI-SD score, VAT, SAT. (ref 15, ref 16)The authors should address these findings. The present study and Giorgio et al 's study were performed in children with NAFLD, Miele et al was performed in adult subjects. Furthermore, the three studies employed different methods of evaluating altered intestinal permeability. One of them investigated SIBO and assessed the integrity of tight junctions in the gut by imunohistochemical analysis, besides evaluating intestinal



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permeability in adult subjects. (Miele et al) Different from the present study they did not measure zonulin and they evaluated BMI and waist circumference for obesity and, for investigation of glucose metabolism and insulin resistance parameters they performed glucose, insulin and HOMA. The other study(Giorgio et al) performed in children with NAFLD used a different test of intestinal permeability from that employed by Miele et al. Also, different from the present study they did not measure zonulin and they evaluated BMI, waist circumference for obesity and the degree of insulin resistance/sensitivity with HOMA IR and with the Insulin Sensitivity Index. The present one measured zonulin, as a marker of intestinal permeability, performed an evaluation of adipose tissue, and of glucose metabolism and insulin sensitivity and resistance. Also important, differences in adjusted variables in correlation analysis with altered intestinal permeability parameters occurred among the three studies. These differences in methods and in the characteristics of the patients make difficult comparisons between the results of three studies. These aspects should be commented by the authors. The cross sectional design of the study precludes a cause-effect relation about severity of steatosis and the presence of NASH and increased zonulin values, only prospective studies can confirm the hypothesis that simple steatosis and NASH are different and not necessarily inter-related diseases. This point should be commented



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ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 11492

Title: Increased circulating zonulin in children and adolescents with biopsy-proven nonalcoholic fatty liver disease

Reviewer code: 00069701

Science editor: Su-Xin Gou

Date sent for review: 2014-05-26 14:05

Date reviewed: 2014-06-05 09:10

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	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"/> Existed	<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"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

COMMENTS TO AUTHORS

1. What is the BMI-SD score, please give the full name when it first appear. 2. What is the update information between zonulin and NAFLD, there are several proteins participate in intestinal permeability, and why are you chose zonulin? 3. In Table 2, please give the full name of MET in the footnote, and the kind of daily physical activities in the questionnaire should be also given in the footnote. 4. Figure 2 showed the zonulin concentrations in the different stage of steatosis, but how do you define the severity of steatosis? And how many subjects are there in the mild, moderate and severe group respectively. 5. Please give some further mechanism about why higher circulating zonulin could be found in patient with NAFLD. 6. Still some miss-spelling, please recheck.