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ESPS PEER REVIEW REPORT

Name of journal: World Journal of Diabetes
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Title: Hepatic glycogenosis: an underdiagnosed complication of diabetes mellitus?
Reviewer code: 02937641
Science editor: Xue-Mei Gong
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CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] Existing	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] No records	
[ ] Grade D: Fair		BPG Search:	[ ] Rejection
[ ] Grade E: Poor	[ ] Grade D: Rejected	[ ] Existing	[Y] Minor revision
		[ ] No records	[ ] Major revision

COMMENTS TO AUTHORS

The text of this short review on hepatic glycogenosis (HG) related to diabetes mellitus is generally well written, but there are three important points which have to be complemented or reconsidered. 1. It is true that "HG is only diagnosed by liver biopsy" as indicated on page 7, third paragraph. It should be mentioned in this context, however, that after conventional tissue preparation (fixation by formaldehyde-solution, staining with H&E) the glycogen is usually eluted from the hepatocytes. Under these conditions, the glycogenotic cells show only an increase in size and a pale or "clear" cytoplasm. It is, thus, mandatory for an appropriate diagnosis of HG that the biopsies are fixed by alcoholic fixatives (such as Carnoy's solution) or shock frozen in advance of the treatment with the periodic acid Schiff-reaction or Best's carmine for the demonstration of the glycogen. In any case, it would be desirable for such a review that examples of the changes described would be documented by figures (preferably with and without demonstration of the glycogen). 2. Fig. 2 is not acceptable as a documentation of HG for two reasons. First of all, the electron microscopic demonstration of an excessive storage of glycogen is not at all mentioned in the text of the manuscript. Although electron microscopic demonstration of glycogen is possible, it is difficult to verify an increase of the glycogen at the ultrastructural level without additional observations in serial sections (e.g. in the tissue blocks used for the preparation of the ultrathin sections) under the light microscope. The second problem with Fig. 2 is that the glycogen has apparently not been contrasted by appropriate procedures (e.g. "staining" by lead hydroxide or lead citrate). Consequently, instead of defined glycogen particles

only "empty" spaces are visible in this figure, in both the cytoplasm and the nucleus. If the authors wish to use an electron micrograph for the demonstration of the glycogen the methods used have to be described in detail in the text and in the legend to the figure. The few mitochondria shown in the insufficient Fig.2 are small, and do not represent "giant mitochondria" as described in the legend to this figure. 3. In the list of diseases which have to be considered in the differential diagnosis of HG (page 7, second paragraph) one important entity is missing: the focal, but sometimes also diffuse, hepatic glycogenosis known for decades to precede the appearance of hepatocellular adenomas and carcinomas (HCC) induced by chemicals, viruses, radiation or oncogenic transgenes in various animal species (see Rec Res Cancer Res Vol 19, Springer, Heidelberg 1968; Biochim Biophys Acta 605, 217-245, 1980; Lab Invest 80, 1399-1411, 2000; World J Gastroentrol 18, 6701-6708, 2012). According to an ever increasing number of observations since 1971 (Virchows Arch A Pathol Anat 352,157-164, 1971, in German; Hepatogastroenterol 34, 10-15, 1987; Pathol Res Practice 190, 513-577, 1994; Hepatology 28, 347-359, 1998; Human Pathol 31, 874-876, 2000; World J Gastroenterol as quoted above; J Hepatol 58, 1147-1156, 2013) this also holds true for human HCC as demonstrated particularly in more than 150 explanted livers from patients suffering from chronic liver diseases prone to develop HCC (Virchows Arch 431, 391-406, 1997). The authors may also be interested to learn that insulin-like effects of the oncogenic agents have been suggested to be responsible for the preneoplastic hepatic glycogenosis (J Bioenerg Biomembr 29, 303-313, 1997; Lab Invest as quoted above; World J Gastroenterol as quoted above). In this context, it is noteworthy that a number of epidemiologic studies have shown that, in addition to inborn hepatic glycogen storage disease (glycogenosis), diabetes mellitus is a risk factor for the development of HCC. The intriguing question whether hepatic glycogenosis related to diabetes mellitus might be involved in the evolution of HCC in diabetes mellit