Answering Reviewers

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Title: Glycogen storage diseases: An update

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We would like to thank the Editor and the reviewers for their time, thoughtful review of the manuscript and constructive criticism. We have carefully made changes accordingly and submitted the revised manuscript. Answers to the questions and suggestions, item by item, were given below.

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Editor:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The author(s) must include the keyword "Liver" in the manuscript title. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the

previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, “Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]”. And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

We thank the editor for the evaluation. Accordingly, we have included the keyword “Liver” in the running title of the manuscript; provided a decomposable Figure as per instructions; added “Copyright ©The Author(s) 2022” in the original figure; reorganized the table as per instructions; used Reference Citation Analysis to further check the bibliography.

Reviewer#1:

Specific Comments to Authors: “The article updates information about the GSD extensively. However the presentation could have been made more appealing. Introduction lacks description about age group affected, clinical relevance,

management issues, need for Multi disciplinary team management, need for surgery etc. and the commonalities of types of GSDs and how they differ among themselves. The GSD types (it is said that there are over 20 types of GSD), could have been classified based on genetic defects, enzymes that are defective, organ affected, incidence, management, and prognosis, etc.; but are enumerated as per serial number. So also similar types are not grouped together and their similarities and differences are not alluded to. Hence very minimal information alone could be provided for types IX to XV. No information is provided about type XIV In the list of involved organs brain is also added, though the neurological manifestations are not due to enzyme deficiency in the said organ In table 1 the columns have no headings and lacks information. Fig-1 do find one sentence in introduction and again left to be interpreted by the reader, including deciphering the abbreviations. It is informed that the aim of the article is to provide comprehensive information about GSDs, especially those with liver involvement but go on to describe all the types. It is conveyed to include GSDs in the DD of patients with "relevant manifestations" but not specified about the manifestations at least in brief."

We thank the reviewer for the comments and constructive criticism that allows us to improve our manuscript.

1. "However the presentation could have been made more appealing. Introduction lacks description about age group affected, clinical relevance, management issues, need for Multi disciplinary team management, need for surgery etc. and the commonalities of types of GSDs and how they differ among themselves."

Although above mentioned features of GSDs are discussed in detail throughout the manuscript under relevant sections, the following sentences have been added to the introduction according to reviewer's suggestion to provide more information also in the introduction.

"GSDs are multisystemic diseases that can present at any age from neonatal period to adulthood."

"Since the initial presenting symptoms can occur in adulthood, it is a group of rare diseases that should be recognized and managed by not only pediatricians but also

physicians taking care of adults. Being multisystemic diseases, GSDs are best managed by a cross-disciplinary approach to achieve good metabolic control, improve the quality of life of patients, and reduce morbidity and mortality[7]. A physician with expertise in managing these disorders (e.g., a metabolic disease specialist, a biochemical geneticist, an endocrinologist, or a hepatologist) should lead and coordinate the patient's care together with a metabolic dietician. Nephrologists, hematologists, genetic counselors, cardiologists, gastroenterologists, neurologists, physical therapists, social workers, and transplant specialists may also be required in the management of a GSD depending on the specific manifestations, complications, and type of the disease."

2. "The GSD types (it is said that there are over 20 types of GSD), could have been classified based on genetic defects, enzymes that are defective, organ affected, incidence, management, and prognosis, etc.; but are enumerated as per serial number. So also similar types are not grouped together and their similarities and differences are not alluded to. Hence very minimal information alone could be provided for types IX to XV. No information is provided about type XIV."

As mentioned in the manuscript there are more than 20 types of GSDs including subtypes, and clinical picture varies dramatically depending on the organ involvement even among patients with the same defective enzyme. The different GSDs are each denoted by a roman numeral that generally reflects the historical sequence of their discovery but not clinical or biochemical similarity. From a practical point of view, we classified GSDs into 2 groups according to primary organ involvement (liver involvement and muscle involvement) as GSD types under each group carry significant similarities regarding not only clinical manifestations but also management strategies. Each phosphorylase kinase subunit is encoded by different genes on different chromosomes and differentially expressed in various tissues. To give an example, GSD type IXd, involving muscle, is written under GSDs that involve the muscle, while other subtypes described in the first part of the review under GSDs that involve primarily liver.

Limited information could be provided regarding type XV as the literature for GSD type XV is very limited. As our knowledge about GSDs increases new types are added to the classification while some are removed from the list. Phosphoglucomutase-1 (PGM1) deficiency (OMIM: 614921), defined as GSD type XIV initially, has later been reclassified as a PGM1-congenital disorder of glycosylation, type It*. Therefore, we did not include it in the review.

* References for GSD type XIV:

- **Perales-Clemente E**, Liedtke K, Studinski A, Radenkovic S, Gavrilov D, Oglesbee D, Matern D, Rinaldo P, Tortorelli S, Morava E, Raymond K. A new D-galactose treatment monitoring index for PGM1-CDG**.** *J Inherit Metab Dis* 2021;**44**:1263-1271 (PMID: 34043239 DOI: 10.1002/jimd.12406)
- https://omim.org/entry/614921

3. "In the list of involved organs brain is also added, though the neurological manifestations are not due to enzyme deficiency in the said organ."

For easy reading and understanding and to give every aspect of the GSD types, the affected organs, whether due to enzyme deficiency or not, are included. In GSD type I, brain involvement may occur as a consequence of recurrent hypoglycemia. On the other hand, it may be directly related to the accumulation of polyglucosan in the brain in GSD type IV. Also, there is a metabolic coupling between astrocytes and neurons in brain regarding glycogen metabolism. Glycogen metabolism in the nervous system was reported to have an important role in normal brain function and in the pathogenesis of neurologic disorders like adult polyglucosan body disease (GSD type IV)*.

- **Benarroch EE**. Glycogen metabolism: metabolic coupling between astrocytes and neurons. *Neurology* 2010;**74**:919-923, 2010 (PMID: 20231669 DOI: 10.1212/WNL.0b013e3181d3e44b.)

4. "In Table 1 the columns have no headings and lacks information. Fig-1 do find one sentence in introduction and again left to be interpreted by the reader, including deciphering the abbreviations."

The column headings in Table 1 were missing when uploading the article and we included headings in the revised version. Figure 1 was cited in the relevant parts of

the article. A detailed explanation of the figure and the used abbreviations were included in the figure legend.

5. "It is informed that the aim of the article is to provide comprehensive information about GSDs, especially those with liver involvement but go on to describe all the types. It is conveyed to include GSDs in the DD of patients with "relevant manifestations" but not specified about the manifestations at least in brief."

We clarified the scope of the study as follows:

"Here, we aim to provide a comprehensive review of GSDs. This review provides general characteristics of all types of GSDs with a focus on those with liver involvement."

We briefly specify "relevant manifestations" in the abstract as follows:

"…relevant manifestations including fasting hypoglycemia, hepatomegaly, hypertransaminasemia, hyperlipidemia, exercise intolerance, muscle cramps/pain, rhabdomyolysis, and muscle weakness."

Reviewer#2:

Specific Comments to Authors: Excellent and comprehensive review but needs few language corrections

We thank the reviewer for the comments that allows us to improve our manuscript. We reviewed the English spelling and grammar of the article with a native speaker and revised when necessary.

Reviewer#3:

Specific Comments to Authors: In this article, the authors aim to update the research progress based on new data and to provide a comprehensive review of GSDs. the manuscript interpret the findings adequately and appropriately and the discussion is accurate.

We thank the reviewer for the comments that allows us to improve our manuscript. We reviewed the English spelling and grammar of the article with a native speaker

and revised when necessary.

Revision reviewer:

Specific Comments to Authors: Thanks for revising the article based on the reviewers comments.

1. However the changes made to the article are not highlighted in the revised article and has to be searched for.

While uploading the revised file to the system, I didn't think that I must upload the article so the changes could be seen. I apologize to the reviewer for that. I had already sent the file (GSD an update-Revision1-changes made to the article are highlighted.docx) where the changes in the first revision can be seen to your e-mail by e-mail.

2. The authors prefer to only enumerate the different GSD types by Roman numerals but has not made any attempt to classify them leaving the task to the reader.

The reviewer wrote that "authors prefer to only enumerate the different GSD types by Roman numerals but has not made any attempt to classify them leaving the task to the reader." As we answered this question previously, the different GSDs are each denoted by a Roman numeral that generally reflects the historical sequence of their discovery but not clinical or biochemical similarity. GSDs are classified mainly into 2 groups according to primary organ involvement (liver involvement and muscle involvement, or both together) as GSD types under each group carry significant similarities regarding not only clinical manifestations but also management strategies. Each type can be divided into subtypes according to the subtype of the enzyme affected and clinical findings. These differences are expressed both in the text and in the table.

3. The tables and figure are separately given rather than incorporated in the article.

The tables and figure had been uploaded seperately as the submission system reuired it.