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Flat C, 23/F., Lucky Plaza,  
315-321 Lockhart Road,  
Wan Chai, Hong Kong, China

## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 9719

**Title:** NAFLD: WHAT HAS CHANGED IN THE TREATMENT SINCE THE BEGINNING?

**Reviewer code:** 02822388

**Science editor:** Gou, Su-Xin

**Date sent for review:** 2014-02-25 12:58

**Date reviewed:** 2014-02-27 13:08

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	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

Please normalized the format before published.



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 9719

**Title:** NAFLD: WHAT HAS CHANGED IN THE TREATMENT SINCE THE BEGINNING?

**Reviewer code:** 02890067

**Science editor:** Gou, Su-Xin

**Date sent for review:** 2014-02-25 12:58

**Date reviewed:** 2014-03-02 23:44

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	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

### COMMENTS TO AUTHORS

Dear Authors I have read this manuscript with a great interest. This topic is of interesting and the manuscript is well-constructed. The article is written in a good English. I have only minor comment to improve this manuscript. What is with angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARBs)? Namely, according to some studies ACE-I and ARBs could be useful therapeutic approach for the patients suffering from NAFLD. I suggest that authors add this in their manuscript in order to improve this manuscript. I suggest the acceptance of this manuscript with this minor comment.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 9719

**Title:** NAFLD: WHAT HAS CHANGED IN THE TREATMENT SINCE THE BEGINNING?

**Reviewer code:** 02541859

**Science editor:** Gou, Su-Xin

**Date sent for review:** 2014-02-25 12:58

**Date reviewed:** 2014-03-05 12:23

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 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	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

NAFLD: What has changed in the treatment since the beginning?

Letter to the author:

It is a good review. I have some comments which are as follows:

Incretin based therapies in the treatment of NAFLD should be mentioned.

In the definition of metabolic syndrome, waist measurement should be given: A waistline of 40 inches or more for men and 35 inches or more for women (measured across the belly)

Genetic factors like PNPLA3 gene polymorphism leading to NAFLD should be mentioned.

In the summary, individualized treatment has been mentioned but not elaborated to the readers.



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## ESPS Peer-review Report

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 9719

Title: NAFLD: WHAT HAS CHANGED IN THE TREATMENT SINCE THE BEGINNING?

Reviewer code: 02861131

Science editor: Gou, Su-Xin

Date sent for review: 2014-02-25 12:58

Date reviewed: 2014-03-06 07:50

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" 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	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

Manuscript Number: 9719 Manuscript Title: NAFLD: WHAT HAS CHANGED IN THE TREATMENT SINCE THE BEGINNING? Confidential Comments To Editor GENERAL COMMENTS (1) The importance of the research and the significance of the research contents; Non-alcoholic liver fatty liver disease (NAFLD) is seen in every geographic region worldwide and it is considered the most common liver disorder in Western countries. More than three decades numerous studies have been conducted which contributed to the better understanding of the NAFLD. Many scientists have tried numerous drugs and alternative medicine, but investigators have failed to present a safe and effective therapy for patients with NAFLD. The evidence based medicine gives us only a few options. The authors of this article have been evaluated the evolution of management of NAFLD in last 30 years. (2) The novelty and innovation of the research; Bülent Baran et al (1) have reported how the traditional “two-hit” mechanism to explain disease progression in NAFLD has been challenged by the novel “multiple parallel hits” hypothesis (2). Although the histopathological picture of steatohepatitis is universal, the evidence behind the “multiple parallel hits” theory indicates that each patient can have shared and distinct pathophysiological stories behind the progression from NAFLD to NASH. In this context, a need for individualized pathogenesis-based approach to medical therapy for patients with NAFLD has been conceptualized in the recent years. The authors have summarized the evolution and current status of different treatment regimens that have been studied in patients with NAFLD. (3) Presentation and readability of the manuscript; Review is well organized, and systematic theoretical analyses and valuable conclusions are provided. This review is a classically presented scientific article. (4) Ethics of the research. Not relevant for this article (this article is review) Bibliography 1. Bülent Baran, Filiz



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Akyüz. NAFLD: what has changed in the treatment since the beginning? *World J Gastroenterol* 2014 in press 2. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. *Hepatology* 2010;52:1836-1846. SPECIFIC COMMENTS Title: accurately reflects the major topic and contents of the study. Abstract: it gives a clear delineation of the research background, objectives and main point presented in this review. As summarized, heterogeneity of pathogenic pathways in individual patients with NAFLD may warrant developing an individualized treatment according to the underlying pathogenic pathway. Review is well organized, and systematic theoretical analyses and valuable conclusions are provided. Introduction: present relevant information about novel "multiple parallel hits" mechanism to explain disease progression in NAFLD which help to elaborate individual pathogenesis-based approach to medical therapy for these patients. Management General principles: present original analysis of lifestyle modifications including dietary changes and exercise targeting significant weight loss that can improve components of NASH. Pharmacologic therapies Insulin sensitizers: present the reason of using of insulin-sensitizing agents in the treatment of NAFLD -Metformin: explain the mechanism of action and suggestion based by novel meta-analyses that not recommended this drug as a primary treatment, especially solely from the standpoint of NASH - -Thiazolidinediones: present analysis of novel studies that recommend - thiazolidinediones, especially pioglitazone, can be used to treat patients with biopsy-proven NASH who have not responded adequately to lifestyle modifications Vitamin E: evaluate the largest randomized controlled study on vitamin E, the PIVENS trial; a newer study, the TONIC trial, included pediatric patients with biopsy-proven NASH; and the recent guideline by American



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**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 9719

**Title:** NAFLD: WHAT HAS CHANGED IN THE TREATMENT SINCE THE BEGINNING?

**Reviewer code:** 02541689

**Science editor:** Gou, Su-Xin

**Date sent for review:** 2014-02-25 12:58

**Date reviewed:** 2014-03-07 03:55

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 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"/> 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 review by Baran et al. covers a relevant topic, however many major concerns should be raised:

- 1) The review provides mainly general informations and sometimes repeated, adding little novelty. E.g. - the pathogenesis section is redundant and not clear. Moreover some relevant concepts have not been treated: e.g. the emerging role of free cholesterol accumulation, SNPs... - therapy section: they omitted to say that physical exercise per se may improve NAFLD, they do not state that rosiglitazone has been withdrawn from the market because increased acute myocardial infarction risk, novel drugs such as incretin-mimetics have not been mentioned.....
- 2) English should be deeply revised throughout the manuscript by an English native speaker.