Dr. Joseph M Pappachan MD, MRCP (London),
World Journal of Diabetes Editorial Board Member ID: 02446526
Department of Endocrinology & Metabolism, University Hospital of North Staffordshire,
Stoke-on-Trent, Staffordshire, ST4 6QG, United Kingdom
E-mail: drpappachan@yahoo.co.in

To
The Editor,
World Journal of Diabetes

01/07/2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name**: 3391 revision)**

Title: Diabetic cardiomyopathy: pathophysiology, diagnostic evaluation and management (Review article)

Authors: Joseph M Pappachan, George I Varughese, Rajagopalan Sriraman, Ganesan Arunagirinathan

Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 3391 Revision

We thank reviewers for their valuable comments and suggestions which we have addressed individually as below and have included changes in the manuscript.

Response to Reviewer 1

Good article summarizing the aspects of diabetic cardiomyopathy

Answer: *Thanks for the comment.*

Responses to Reviewer 2

1. **The importance of the research and the significance of the research contents;**

Comment: The current manuscript presents an interesting, integrative research on diabeteic cardiomyopathy, in terms of its inducing factors, pathogenesis, diagnostic and therapeutic perspectives. It is interesting and additive for professionals in the field of metabolic, ednocrine and cardiovasacular diseases and therapeutics.

Answer: *Thanks for the comment.*

2. **The novelty and innovation of the research;**

Comment: Actually several reports presented similar approaches, e.g.
Chavali V, Tyagi SC, Mishra PK.
Predictors and prevention of diabetic cardiomyopathy. Diabetes Metab Syndr Obes. 2013 Apr 11;6:151-60.
I recommend reading the indicated review and create your own spirit in your review.

Answer: *We read this paper and appropriate changes (highlighted in red fond) were made in the revision. The paper is also referenced in the revision*

3. **Presentation and readability of the manuscript;**

Comment: the readability and flow of presentation is good, however an improvement of English language is necessary.

Answer: *The language has been revised and appropriate changes are made and highlighted in red fond in the revision.*

4. Ethics of the research; **N/A**

SPECIFIC COMMENTS

1. **Under the title of lipid metabolism and the myocardium**;

The mechanism by which FFA induces insulin resistance is missing, which is through the protein kinase C (PKC) pathway. PKC (a serine/threonine kinase) phosphorylates inhibitor of kappa light polypeptide gene enhancers B- cells (IkKB) kinase, and this in turn phosphorylates insulin receptor substrate-1 (IRS-1 Another mechanism of FFA-mediated insulin resistance is via peroxisome proliferator-activated receptor (PPAR)-γ and (PPAR-α) . Kindly elaborate on these issues.

Answer: *necessary changes has been made and highlighted in red fond.*

2. ***Diagnostic evaluation of DbCM and its remodeling.***

The paragraph of the staging of the DbCM needed some clarifications, that are added in the attached amended manuscript. Kindly modify according to the corrections in red.

Answer: *Appropriate changes are made in the revision and they are highlighted in red fond.*

3. **Diagnostic evaluation of DbCM** lacked heart catherisation and coronary angiography. Kindly discuss these thoroughly.

   Answer: *these changes are made in the revision and highlighted*

4. **The serological cardiac markers** is missing " Troponin", the reliable contractile protein for diagnosis of myocardial infarction. Also the new micro RNA(miRNAs) should be discussed.

   Answer: *these are discussed and changes are made in the revision and highlighted*

5. **The therapeutic measures for DbCM** should be thoroughly discussed. There is no mention to the insulin sensitizers and their role for the prevention for diabetic, hence vascular heath and cardiovascular prevention.

Kinldy mention the following treatment approaches;
a. Metformin for T2D
b. Insulin for T1D
c. Pioglitazone (mitigates diastolic dysfunction)
d. Beta-blocker (decreases hypertension)
e. Angioplasty (for microangiopathy and coronary stenosis
f. miRNA treatment?
g. Stem cell therapy?

Dipeptidylpeptidase inhibitor (DPP-I) are also among the newest therapeutic strategies. Kindly elaborate more….. Incretin and Amylin mimetics have been recently attracted the investigational attention. Kindly elaborate more. Glucagon-like peptide (GLP)-1 is an incretin hormone that stimulates postprandial insulin secretion and improves insulin sensitivity. Individuals treated with GLP-1 also have improved left ventricular ejection fraction.
Highlights on the newest therapeutic antidiabetic approaches, especially the combinational therapies (Sitagliptin + Metformin; Sitagliptin + Statins) would add to the therapy- entity in their review.

Answer: *All these topics are discussed and necessary changes are made in the revision which are highlighted in red fond.*

Response to Editors comments

All comments by the editor have been addressed and necessary changes have been made in the revision as suggested.

WL1-WL3: changes were done and highlighted in red in the revision
WL4: Appropriate PMID and DOI (where available) are included in the revision
WL5 & WL6: Separate decompossible figures are uploaded as separate power point file.

We hope these changes meet the requirements of the *WJD*.

Sincerely yours,

On behalf of all the authors

Dr. Joseph M Pappachan,
01/07/2013