Dear Editors

Thank you very much for your email with which you sent us the reviewers’ comments on our paper. We also wish to take this opportunity to thank the reviewer for his constructive comments and valuable recommendations. The comments have been carefully taken into account and a new revised submission have been uploaded. We responded point by point to the comments.

Our responses are listed below:

Reviewer #1:

Comments: In this study, the authors show how dietary CML alters myocardial glucose metabolism and cardiac remodelling in vivo and in vitro. To date, this is the first study in which CML is related to myocardial remodelling. The topic is interesting, although the overall background of the manuscript should be improved, in particular about CML and myocardial remodelling. This manuscript in present form doesn’t adequately describe the background and the present status and significance of the study. Also the limitation and future direction of the study should be added.

Answering: Thank you very much for your review. We have read your comments very carefully. And according to your comments, we extensively revised this manuscript.

We add the background of the study in the ‘BACKGROUND’ of ‘ABSTRACT’ (Page 2).

‘Myocardial remodeling is a key factor in the progression of cardiovascular disease to the end-stage. In addition to myocardial infarction or stress overload, dietary factors have recently been considered associated with myocardial remodeling. Ne-(carboxymethyl)lysine (CML) is a representative foodborne toxic product, which can be ingested via daily diet. Therefore, there is a marked need for exploring the effect of dietary CML on the myocardium.’
We add the background and present status of the study in INTRODUCTION section (Page 4, paragraph 1).

‘Cardiac remodeling is characterized by cardiomyocyte hypertrophy, apoptosis, fibrosis, and increased fibrocollagen deposition [3]. Short-term compensatory remodeling increases cardiac contractility, while long-term sustained pathological remodeling leads to a decline in cardiac function or even heart failure [4]. Cardiac remodeling can be caused by myocardial infarction, stress overload, inflammatory cardiomyopathy, idiopathic dilated cardiomyopathy, or diabetes [5]. Although these causes differ, they share similar mechanisms such as oxidative stress, endoplasmic reticulum stress and inflammatory response [6].’

We add present status of the study in the INTRODUCTION section (Page 4, paragraph 2 and 3)

‘Nakamura et al. found that carbohydrate content in the diet could affect myocardial remodeling [9]. Zeng and his colleagues reported that a high-fat diet promoted myocardial remodeling [10].’

‘The dietary intake of CML was positively correlated with prevalent vertebral fractures [20].’

We edit INTRODUCTION section (Page 4, Paragraph 3) to make it more logical and emphasize that importance of the study

‘Advanced glycation end products (AGEs) are a class of heterogeneous irreversible products formed by non-enzymatic reactions [11]. AGEs can accumulate in various tissues resulting in adverse health effects by increasing disease pathogenesis [12,13]. AGEs can accumulate via endogenous and exogenous mechanisms. Food is the main source of exogenous AGEs [14]. Nϵ-(carboxymethyl)lysine (CML) was considered a representative of food-derived AGEs [15]. CML has been found in a variety of foods such as milk, bakery products and coffee. Ahmed et al. reported that the concentration of CML was 877 ± 47 nM in pasteurized milk [16]. Assar et al. reported that bread crust contained 46.1 mg/kg of CML [17]. Ingestion of CML via routine diet is substantially higher than the level of CML in plasma and tissues [18]. Daily exposure to high levels of CML is a health risk for humans [19]. …… However, it is currently unknown whether CML intake affects myocardial remodeling.’
We add the limitation and future direction of the study in DISCUSSION section (Page 14, Paragraph 2).

‘We investigated the detrimental effects of dietary CML on myocardial remodeling to draw attention to the CML content in the diet. However, this study has some limitations. The exploration of specific mechanisms needs to be further continued in the future, and clinical evidence is also needed. We speculate that dietary CML may also promote myocardial remodeling through non-receptor and receptor approaches. CML could increase collagen cross-linking in the extracellular matrix and bind to its receptors to activate related signals. In the future, we will further explore the mechanism of cardiac remodeling induced by dietary CML to identify effective targets for intervention. There is an endogenous CML generation system in human body. Compared with reducing endogenous CML, reducing exogenous CML from dietary sources appears to be more controllable. Previous studies have also reported some CML inhibitors, such as antioxidants and aminoguanidine [15]. However, these additives may change the original methods of food production, and their high cost and unclear safety also limit the application. Therefore, in the future, we will also focus on strategies to inhibit CML in diet preparation.’