The manuscript submitted by Dr. Li et al. gave a comprehensive review of the application of the metal-organic framework in diabetes. This review is systematic and well-organized, which provides a valuable summary and will guide future studies on this topic. The reviewer only has some minor points:

1) The grammar of the title is not correct. “its” should be replaced by “their”. It’s actually better to delete “wound healing” from the title because wound healing is already included in the treatment of diabetes.

Response 1: The title of the manuscript was changed from "Application of metal-organic framework in diagnosis and treatment of diabetes and its wound healing" to "Application of metal-organic framework in diagnosis and treatment of diabetes".

2) All figures are too small. It’s very hard to recognize captions in such a small figure.

Response 2: We have updated the figure throughout the article, changing the font and size in the figure to improve the clarity of the figure.**(Figure 1-9)**

3) The “Biomimetic mineralization” should be added to Table 1 as a synthetic method. Refer to https://www.nature.com/articles/ncomms8240.

Response 3: We have added the content of biomimetic mineralization in Table.1, and made corresponding adjustments in the content of the manuscript. The red font is the new content. **(Line 77, 126-138)**

Table 1. Comparison of advantages and disadvantages of MOFs synthesis methods.

Synthetic methods	Advantages	Disadvantages	Ref.
Hydrothermal/solvothermal synthesis	Generality, simplicity and low cost. Can large-scale preparation at mild temperatures.	Long reaction time, high temperature requirement	[22, 27,28]
Microwave-assisted synthesis	Shorten the reaction time to a few hours or even several minutes. No excessive by-products, and the high purity and small size of MOFs obtained.	Reaction solvent requirements are limited	[29-31]
Room temperature synthesis	Reaction conditions are simple and can be prepared on a large scale.	Limited range of adaptation	[32,33]
Ultrasonic-assisted synthesis	Quickly disperse solutes and speed up the reaction process, improve the reaction	Hard to get a lot of product	[34,35]

	efficiency.		
Mechanochemical synthesis	Safety, environmental protection	Hard to get a lot of product	[36,37]
Microfluidic synthesis	The effective mixing of organic phase and inorganic phase is realized.	Limited range of adaptation	[38,39]
Biomimetic mineralization	Beneficial to enhance the robustness, biocompatibility and biocompatibility of biomacromolecules.	Only suitable for biomacromolecules that are similar in size to the pore size of MOFs and are solvent resistant in the preparation of MOFs.	[25,26,40]

"2.7 Biomineralization synthesis"

Biomineralization refers to the process of generating inorganic minerals by organisms through the regulation of biological macromolecules. Under certain physical and chemical conditions, proteins, enzymes and DNA can rapidly induce the formation of protective metal organic framework coatings by converting ions in solution into solid minerals under the control or influence of biological organic substances[25,26]. Biomimetic mineralization provides unprecedented protection from biological, thermal, and chemical degradation while maintaining biological activity by encapsulating biological macromolecules in porous metal-organic frameworks[52]. He et al. combined a low-cytotoxic and pH-sensitive biodegradable MOF material (Zeolitic imidazole framework-8 (ZIF-8)) with insulin (INS), GOx and catalase (CAT) co-loaded to form glucose-responsive NPs as functional "cores", enabling long-term glucose-responsive insulin delivery[40].

4) Insulin is a pH and enzyme-sensitive protein and is usually injected subcutaneously. For section 4. 1 oral insulin delivery, can you elaborate more rationale and mechanism of using MOF as the delivery vehicle and protective shields? Especially how the use of MOF can protect insulins from pH and enzymatic digestion?

Response 4: The red font is new content to answer the principle and mechanism of MOF as drug delivery carrier and protective shield. **(Line 287-295,Line 298-308)**

"4.1 Oral insulin delivery"

Direct injection of INS is currently the only effective treatment for diabetes[95]. INS has a short blood half-life, requires intensive self-management by patients during injection, and frequently adjusts the dose according to Blood Glucose Level (BGL) monitoring. Long-term injection can lead to local tissue necrosis, nerve damage, and microbial infection[96]. Therefore, it is necessary to develop other types of INS delivery methods. Oral in-sulin is associated with better patient compliance than injection. However, INS is a pH and enzyme-sensitive protein. It is well known that the main challenges of oral INS delivery strategies include, on the one hand, the strongly acidic environment in the stomach and pepsin-mediated degradation, as well as digestive enzyme-mediated degradation in the gut. On the other hand, it is the low permeability of protein drugs across the gut biomembrane

that results in low bioavailability[97,98]. Both mucous cells and epithelial cells in the gut act as barriers. Therefore, an optimal oral delivery system should not only protect insulin from degradation in the gastrointestinal environment, but also promote its permeability through intestinal epithelial cells. The alkaline environment of the gut may increase the availability of therapeutically active ingredients and can transport them directly to the systemic circulation through the hepatic hilum or the intes-tinal lymphatic system[99].

As early as 1993, Archibald et al. proposed the concept of biomineralization to achieve high-fidelity replication and functional specificity of biomaterials and biopolymers[100]. The most typical biomineralization product is the formation of MOFs complexes. MOFs have emerged as a promising class of proteins by confining proteins within their rigid frameworks with tunable mesoporous structures, high surface area and water stabil-ity, while achieving high loadings while significantly improving the thermal and chemi-cal stability of encapsulated proteins functional protein immobilization and storage ma-terials[101,102]. Through the uniform mesoporous structure, the loading and release of insu-lin can be flexibly controlled.

The combination of MOFs with other materials (such as hydrogels, microspheres, proteins, etc.) will enable MOFs to have multiple functions. In the latest study, Rojas et al. synthesized CS@MIL-127 as drug delivery systems (DDSs), which exploited the good bio-compatibility, large porosity, and excellent stability along the gastrointestinal tract of mi-croporous iron-based nanoMOFs[99]. In addition, the use of biopolymer chitosan greatly improved the intestinal permeaility of MIL-127, and the safety and efficacy of the DDSs were confirmed using *C. elegans*.(Fig. 5A) Zhou et al. developed a novel nanocomposite carrier (Ins@MIL100/SDS@MS) based on iron-based MOF nanoparticles (NP) (MIL-100) with high loading of biodegradable microspheres for oral INS delivery[103]. (Fig. 5B) The microspheres effectively protected MOF NPs from rapid degradation under acidic condi-tions and could release INS-loaded MOF NPs in simulated intestinal fluid. Chen et al. used Zr6-based mesoporous MOF NU-1000 as a carrier for INS, and achieved rapid en-capsulation and stabilization of INS within 30 min[104]. (Fig. 5C) To further improve the delivery efficiency of INS, Jun et al. designed an acid-resistant nMOFs (UiO-68-NH_2) with external targeting protein (Tf) modification for efficient oral INS administration[105]. (Fig. 5D) Among them, UiO-68-NH2 has high porosity, acid stability and phosphate ion insta-bility. Decorating the exterior of UiO-68-NH_2 with a targeting protein (transferrin) can simultaneously protect insulin from acid and enzymatic degradation, resulting in an effi-cient oral INS delivery.