

Dear the peer reviewers:

First of all, thank you very much for the review of our manuscript and your support.

Next, we will answer your question as follows.

1. Is the sphincter disturbance related to the physical presence of stones rather than their composition?

Our research shows that pigment gallstone-causing diet and cholesterol gallstone-causing diet can induce the sphincter disturbance. High cholesterol diet can cause hypercholesterolemia and a cholesterol metabolic disorder might induce the sphincter dysfunction. Related studies have been reported that hypercholesterolemia could cause sphincter of Oddi dysfunction (SOD). However, there were different opinions about whether or not the sphincter disturbance is related to the physical presence of stones. Quallich et al suggested that bile duct crystals do not contribute to SOD, but Kuo et al considered stones in the common duct might injure or irritate the SO and cause SOD.

2.myoelectric frequency also surprising?

SO manometry (SOM) is the only method to directly assess the motor function of the SO and is considered the gold standard for assessing SOD. But manometry changes of SO in

cholelithiasis are quite controversial. Research of Pang et al indicted a significant increase in the base pressure of the SO in rabbits with cholesterol lithogenic diet. On the contrary, study in prairie dogs showed SO resistances remained normal throughout the period of gallstone formation. Meanwhile, the mechanical activity recorded may not represent the features of SO activity especially in the relaxed SO. Another measurement reflecting SO function is recording of myoelectric activity of SO.

The earliest SO electrophysiological study was the impact of gastrointestinal hormone on SO myoelectric activity in 1975. They found that cholecystokinin, Frog skin pigment and gastrin could promote SO myoelectric activity and increase the SO amplitude, and glucagon could decrease SO myoelectric activity. A recent study indicated that SO myoelectric activity decreased significantly in a rabbit model of chronic cholangitis. Our study explored changes in SO pressure and SO myoelectrical activity in the process of pigment and cholesterol gallstone formation, contrasted their sensitivity, and compared their advantages and disadvantages in the study about SO motility. In this study, SOM and myoelectric activity of SO was investigated simultaneously at different stage of stone formation. SO myoelectric activity analysis indicated that

frequency and amplitude of myoelectric activity decreased apparently in the 9w group. Following SO manometry analysis also showed the same result that both SO amplitude and SO frequency decreased significantly in the 9w group.

3. The results section has been added to the 3 and 6 week results and why CCK-8 was not increased has been discussed.

If you have any questions, please inform me. Thank you once again.