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Entrapping digestive enzymes with engineered silica particles reduces metabolic risk factors – evidence from preclinical and clinical investigations

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Mesoporous silica particles (MSPs) are thermally and chemically stable porous materials composed of pure silica and have attracted substantial attention for their potential uses in biomedical applications1,2. By carefully tailoring the MSP characteristics (controlled surface area, pore volume, pore size, particle size and morphology), we have engineered a silica particle (SiPore15™) that efficiently entraps key gastrointestinal digestive enzymes (Figure A and B). Preclinical investigations illustrate how pancreatic lipase and α-amylase are sequestered by SiPore15™ in vitro (Figure C). This phenomenon is also demonstrated in a mouse intestine model ex vivo, where the enzyme activity in the SiPore15™ exposed murine duodenal fluid is substantially decreased3. We hypothesize that SiPore15™ acts by lowering the enzyme activity in the small intestine, subsequently resulting in decreased digestion of macronutrients, leading to reduced calorific uptake at the organism level 4. To date, 60 human subjects have been orally treated with 9 g/day of SiPore15™. A First-in-Man (FiM) trial has been completed with healthy volunteers (n=10) and obese participants (n=10). The clinical effects observed in the obese participants were significant reduction in metabolic and cardiovascular risk factors such as HbA1c (net reduction of 1.7 mmol/ml, - 5%) and LDL-cholesterol (net reduction of 0.4 mmol/L, - 15%) (Figure D). The observed adverse events were mild and transient 5. SiPore15™'s innovative mode of action, combined with the effects observed in obese subjects and the promising safety profile, makes SiPore15™ an exciting candidate for treatment/prevention of metabolic diseases. A second trial with prediabetic/type 2 diabetes patients (n=40) is ongoing and the results will be reported in the second half of 2019 (clinicaltrials.org ID no. NCT03823027).

Discussion: In our recent clinical study, we concluded that oral intake of MSP is safe and well tolerated and the details of these findings are reported elsewhere (E. Hagman, A. Elimam, N. Kupferschmidt, K. Ekbom, S. Rössner, M. N. Iqbal, E. V. Johnston, M. Lindgren, T. Bengtsson, P. Danielsson, submitted manuscript). In the same study we observed improved glucose and lipid homoeostasis, data reported herein (Figure 2) together with preclinical findings supporting a postulated mechanism of action. These clinical observations, together with preclinical data on reduced weight gain in mice, led us to envisage a novel therapeutic principle. We hypothesized that oral intake of MSP with a defined pore size would sequester digestive enzymes in the GI tract. This would result in reduced food digestion, reduced energy uptake, and improvement of metabolic parameters.

Here we show that treating human obese subjects for 12 weeks with MSP lead to an average 1.7 mmol mol−1 decrease in the long-term blood glucose marker HbA1c. It is important to keep in mind that the study was designed to address safety and not to study effects on metabolic markers. The subjects with obesity studied herein had normal baseline HbA1c levels and did not have T2D. Thus the results herein cannot be directly compared to studies with higher HbA1c baseline levels, as this is known to result in more pronounced effects on HbA1c. Still, it is interesting that studies with the most commonly used antiobesity drug Orlistat (lipase inhibitor) suggest an ≈4 mmol mol−1 reduction in HbA1c in subjects that have both obesity and T2D. Moreover, diabetes prevention studies have looked at the effect of Metformin, a common T2D drug, on HbA1c in populations similar to the one studied here and have found that a reduction of 1.0–1.6 mmol mol−1 significantly reduced the risk of developing diabetes. Furthermore, we anticipate that in a population with higher basal HbA1c level such as subjects with T2D, the effect of MSP treatment would be greater. Even with the small number of study subjects reported here, we observed a statistically significant reduction in LDL cholesterol already after 3 weeks, with a further decrease after 12 weeks (average decrease of 0.4 mmol L−1). A reasonable comparison could be with statins, the most common LDL lowering drugs. In a large meta-analysis, statins decrease LDL on average by 1.09 mmol L−1 after one year of treatment.[33] Again, the exact comparison is uneven, since our subjects were only treated for 3 months and had normal LDL baseline levels. Another comparison could be with large numbers of Orlistat treated (lipase inhibitor) individuals with obesity, showing LDL cholesterol reductions in the 0.21–0.47 mmol L−1 range.

There are likely a number of factors influencing the MSP-mediated effects in humans, such as dietary pattern, meal composition, lifestyle, physiological factors, and pathological conditions. The number of subjects treated in this study is small, therefore it can only be speculated as to why there are individual differences in the MSP mediated responses in HbA1c and LDL. The individual variation in HbA1c/LDL reduction seen here could be explained by changes in gross dietary intake, as it is not controlled for here.

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