Fried Foods, Gut Microbiota, and Glucose Metabolism

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Hot oil–based frying is a popular cooking method that makes food more appealing in texture and aromatic, thus improving palatability. Fried foods are considered unhealthy because frying may increase the energy density of foods and therefore energy intakes as well as deteriorate oils through the process of oxidation and hydrogenation, leading to a loss of unsaturated fatty acids such as linoleic and linolenic acids but increase in *trans* fatty acids, oil degradation, and advanced glycation end products (1,2). In epidemiological studies, high intakes of fried foods have been associated with a variety of adverse health outcomes including type 2 diabetes (T2D), although the results are not entirely consistent (3–6). The conflicting findings are partly due to the diverse types of oil used in frying foods. For instance, null associations between fried foods and T2D risk were reported in populations with fried foods prepared using mainly olive oil, which is more resistant to oxidation than other common oils used for frying such as corn oil (4). In addition, the varying compositions of the foods being fried and frying conditions (temperature, duration) may also trigger the heterogeneous results. An extra layer of complexity in the inconsistent observations is introduced by various confounding factors such as weight gain, high blood pressure, and lipidemia, which are correlated with both fried food consumption and T2D risk (1,7). The causality of fried foods in glucose dysregulation and the development of T2D could only be detected in investigations in which the cofounding was rigorously controlled, such as randomized clinical trials.

In addition, the potential mechanisms underlying the observed adverse associations between fried foods and T2D remain largely unknown; previous studies suggest that a myriad of pathways such as weight gain, inflammation, and lipid metabolism may be involved (1,2). In recent years, growing data suggest that the gut microbiota may play a key role in linking dietary factors including fried foods and host's health (8,9). Studies in humans and animal models indicate that fried food consumption or the byproducts of frying and thermal processing are related to the diversity and richness of the gut microbiota (10,11). However, the randomized clinical trials assessing the effects of fried foods on the gut microbiota and the subsequent glucose metabolism are still lacking.

In this issue of *Diabetes Care*, Gao et al. (12) present the results from a randomized controlled feeding trial to test the effects of fried meat intakes on glucose homeostasis. A total of 117 young overweight (BMI >24 kg/m^2) adults aged 18–35 years were randomized into two groups, which were provided isocaloric meals with consistent foods and the Alternate Health Eating Index (AHEI) score >85, but different meat cooking methods—frying in the intervention group and boiling, streaming, or dressing with sauce in the control group. It is noted that several indices of glucose metabolism including the insulinogenic index (IGI), muscle insulin resistance index (MIRI), and insulin levels were improved during the intervention in both groups, along with the reduction of energy intake. Compared with the control group, the 4-week intervention by fried foods group showed less improvement in IGI, MIRI, and area under the curve (AUC) of insulin, and no difference in HbA_{1c}, C-peptide, and AUC of glucose. The authors concluded that fried meat intake impaired glucose homeostasis.

Among the secondary outcomes, the group with fried meat intervention showed less reduction in biomarkers of intestinal endotoxin and systemic inflammation and less increase in FGF21, a hepatokine regulating satiety and sugar intake (13). In addition, it was found that the fried meat group had a lower gut microbiota richness than the control group; the overall microbial structure and composition as well as the microbiota-predicted pathways relating to glucose homeostasis were also different between these two groups. Notably, the ratio of *Firmicutes* and *Bacteroidetes*, a traditional marker of T2D (14), was higher in the intervention group than the control group. In addition, fried meat intervention led to significant shifts in fecal cometabolites, such as decrease of butyric acid, valeric acid, and indole-3-propionic acid and increase of carnitine. Changes in these fecal metabolites showed significant correlations with changes in IGI, MIRI, intestinal endotoxin lipopolysaccharides, FGF21,

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and inflammatory biomarkers, implying the compound mechanistic connections between the gut microbiota and glucose homeostasis. The findings were further supported by the experiment in mice.

This study by Gao et al. has several major strengths. Randomized clinical trials are considered the gold standard to provide evidence for causality. In the study by Gao et al., the foods tested were carefully controlled and consistent in the intervention and control groups, and randomization minimized the potential confounding. Therefore, the observed differences in the primary outcomes related to glucose homeostasis were likely caused by the distinct food processing method—frying. Novel to this study is the integration of profiling the gut microbiome with quantitatively targeted bacterial metabolomics in the fecal samples. Such analyses provide novel evidence for the roles of the microbial community in mediating the dietary effects on glucose metabolism. In addition, the experiments in mice provided extra proof to the findings. The comprehensive assessment of a broad range of biomarkers including intestinal endotoxin, systemic inflammation, and others further contribute to our understanding of the complex bonds between fried meat, gut microbiota, and glucose metabolism.

The study is subject to several potential limitations. Given the relatively short term of intervention, the study could not evaluate the prolonged effect of fried foods on glycemic homeostasis and T2D risk. Notably, the primary outcomes, including glucose and HbA_{1c}, did not differ between the intervention and control groups. This might be partly due to the short intervention and relatively small sample size. The study participants are relatively young and healthy; therefore, the generalizability of the findings is constrained. In addition, the ancillary nature and multiple testing in analyses justify cautions against making causal inference on the findings of the biomarkers and microbiome.

The findings from the study by Gao et al. reemphasize the importance of investigating the causal and mechanistic links between the diet, gut microbiota, and T2D, which have been evidenced by the growing studies in the past 10 years (15–18). Compelling data have shown that the gut microbiota may affect host's health mainly through circulating metabolites (19). The gut microbiota takes a critical part in the digestion of food ingredients, and a significant proportion of the blood metabolome reacts to the ingestion of foods. Therefore, circulating metabolites directly symbol the host-microbiota-diet interactions (17,20). In addition, emerging evidence indicates that dietary interventions may significantly change circulating microbial metabolites and subsequently affect glucose metabolism (21,22). Thus, comprehensive analysis of circulating metabolome is called for in the future randomized clinical trials. Further investigations are also warranted to assess the effects of fried foods by various types of oil, as prior data suggest foods fried in certain types of oil such as extra virgin olive oil may improve postprandial insulin response (23). The evidence from the study by Gao et al. may contribute to draw more attention on the inclusion of the healthy food processing methods in the dietary guidelines, beyond the nutrients and food components. Food processing is largely overlooked in the current dietary recommendations. Notably, the beneficial effects of healthy foods such as vegetables may be diminished during frying at high temperature (24). Therefore, the future dietary guidelines would take the food processing methods into account.

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