# Endocrine

The Genetic Basis of High-Carbohydrate and High-MSG Diet Related to the Increase of Likelihood of Type 2 Diabetes Mellitus: A Review

---Manuscript Draft---

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<td>Abstract:</td>
<td>Diabetes is one of the most common metabolic diseases. Aside from the genetic factor, previous studies stated that other factors such as environment, lifestyle, and paternal-maternal condition play critical roles in diabetes through DNA methylation in specific areas of the genome. One of diabetic cases is caused by insulin resistance and changing the homeostasis of blood glucose control so glucose concentration stood beyond normal rate (hyperglycemia). High fat diet has been frequently studied and linked to triggering diabetes. However, most Asians consume rice (or food with high carbohydrate) and food with monosodium glutamate (MSG). This habit could lead to pathophysiology of Type 2 Diabetes Mellitus (T2D). Previous studies showed that high-carbohydrate or high-MSG diet could change gene expression or modify protein activity in body metabolism. This imbalanced metabolism can lead to pleiotropic effects of diabetes mellitus. In this study, the authors have attempted to relate various changes in genes expression or protein activity to the high-carbohydrate and high-MSG induced diabetes. The authors have also tried to relate several genes that contribute to pathophysiology of T2D and proposed several ideas of genes as markers and target for curing people with T2D. These are done by investigating altered activities of various genes that cause or are caused by diabetes. These genes are selected based on their roles in pathophysiology of T2D.</td>
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<td>When revising your work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Your revision is due by 25 Feb 2020.</td>
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You will see a menu item called 'Submissions Needing Revision'. You will find your submission record there.

Please make sure to submit your editable source files (i.e. Word, tex).

Yours sincerely,
Sebastiano Filetti
Editor-in-Chief
Endocrine

COMMENTS FOR THE AUTHOR:

Reviewer #1: 1- MSG (monosodium glutamate) as an abbreviation should be spelled out in the title as well as the abstract and should be added into the abbreviation list. Moreover, MSG should be spelled out when it is first mentioned then only MSG and not monosodium glutamate should be used later. This should be done for all the used abbreviations.
Reply: MSG and T2D in the title, and abstract have been prolonged for the first time. However, for the gene name, we still use the abbreviations.

2- The manuscript should be revised for linguistic and grammatical mistakes as well as typographical errors e.g. the authors (in the abstract), dephosphorilation of FoxO1 (in Figure 1) and in page 5 line 119 “Scd1 deficient alone …” should be “Scd1 deficiency alone …”.
Reply: We are grateful for the input. We change the figure 1 also ask Mrs Helen to recheck and do some proofread on the manuscript.

3- The authors stated that high carbohydrate diet plus high intake of MSG contribute to the emergence of type 2 diabetes. The authors should differentiate between correlation and causation. The authors should show which studies revealed only that the prevalence of type 2 diabetes is correlated with high carbohydrate diet and high intake of MSG and which studies investigated the possibility that high carbohydrate diet and high intake of MSG could lead to type 2 diabetes.
Reply: We deleted the sentence “both factors combine to increase risk of T2D” in the introduction. We noticed that we have to tone down this sentence. Therefore, we just put this as hypothesis that might be interesting to be investigated in animal studies in the last paragraph in the genetic aspects section (before entering human population study).
For genetic aspects, such as in Table 1, we already wrote that for genes which affects T2D development, it is highly probable that disruption of those genes by imbalance diet could lead to the onset of hyperglycemia. As for changed by T2D, then the hyperglycemic period happen first that lead to the change to gene expression. However, indeed many genes are still on the side of N.D., which is the there is missing link on the time period of the activation of the phenotypes. Meanwhile, it can be also caused by a feedback loop from the activation / suppression of the genes itself that create vicious cycle. Also to give balance to the experimental data, we then added a new section about human-population study. This will describe more about the correlation between lifestyle and diet to the metabolic disorders. We also added several sentences in the MSG section and in the epidemiology studies that highlighted the main difference in the treatment for MSG case, in which in various animal, genetic, and experimental studies, the model was created by MSG injection, and not by feeding.

4- Are there any studies showing non-significant correlation between the prevalence of type 2 diabetes is and high carbohydrate diet as well as high intake of MSG? You should show all relevant studies!!
Reply: We added some results from epigenetic studies related to the onset of T2D due to high-carbohydrate diet and high-MSG diet. We also added a new section related to a more comprehensive epidemiological data so that the experimental data can be
compared with population-based study and gave a bigger picture of the status quo on both high-carbo and high-MSG. Indeed, despite various factors plays in the epidemiological study, major results for high-carbohydrate diet is positively correlated with diabetes and could also gave rise to diabetes for a healthy patient. But for high-MSG diet, many results are in conflict to each other. We also tried to give some explanation to this in the new section and also in the first paragraph of the impact of MSG by describing the fate of MSG in the gut and why MSG can be considered GRAS as food additive.

5- It would be great if the authors can explain the strategy they used to pick up the genes to be discussed in this review.
Reply: New sentences are added in the last paragraph of the introduction to explain basic ideas on how we screen some genes and gather the articles to assign the review.

6- I suggest adding a small paragraph about the fate (absorption and metabolism) of MSG after its ingestion.
Reply: A new paragraph is added in the impact of MSG section as its first paragraph (line 173-179). There, we describe how MSG can be considered GRAS as food additive We also added a new paragraph after the section to differentiate that various genetic and experimental data employed either MSG injection (subcutan or peritoneal) or by cell culture not by feeding.

7- The authors should also mention epigenetic mechanism leading to insulin resistance by referring to: J Hypertens. 2019;37(11):2123-2134. doi:10.1097/HJH.0000000000002156. Is something known about epigenetic mechanisms of High-Carbohydrate and High-MSG Diet induced insulin resistance? Reply: Epigenetic experimental data have been added in the introduction, such as famine, related to low birth weight, imbalance diet, fetal programming by impaired maternal.

8- In Figure 3, what is the relation between the factors in the upper part of the figure and the term "MSG induced".
Reply: it has been corrected to

9- The authors should spell out MSG in the title. In general, use rather full names then abbreviations.
Reply: It is corrected.
The Genetic Basis of High-Carbohydrate and High-Monosodium Glutamate Diet Related to the Increase of Likelihood of Type 2 Diabetes Mellitus: A Review

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Abstract

Diabetes is one of the most common metabolic diseases. Aside from the genetic factor, previous studies stated that other factors such as environment, lifestyle, and paternal-maternal condition play critical roles in diabetes through DNA methylation in specific areas of the genome. One of diabetic cases is caused by insulin resistance and changing the homeostasis of blood glucose control so glucose concentration stood beyond normal rate (hyperglycemia). High fat diet has been frequently studied and linked to triggering diabetes. However, most Asians consume rice (or food with high carbohydrate) and food with monosodium glutamate (MSG). This habit could lead to pathophysiology of Type 2 Diabetes Mellitus (T2D). Previous studies showed that high-carbohydrate or high-MSG diet could change gene expression or modify protein activity in body metabolism. This imbalanced metabolism can lead to pleiotropic effects of diabetes mellitus. In this study, the authors have attempted to relate various changes in genes expression or protein activity to the high-carbohydrate and high-MSG induced diabetes. The authors have also tried to relate several genes that contribute to pathophysiology of T2D and proposed several ideas of genes as markers and target for curing people with T2D. These are done by investigating altered activities of various genes that cause or are caused by diabetes. These genes are selected based on their roles in pathophysiology of T2D.

Keywords: gene expression, high carbohydrate, insulin resistance, metabolism, monosodium glutamate, obesity, regulatory protein, type 2 diabetes mellitus.

Abbreviations

<table>
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<th>Abbreviation</th>
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<tr>
<td>GLUT4</td>
<td>Glucose transporter 4</td>
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<tr>
<td>PDX1</td>
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<tr>
<td>NKX6.1</td>
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<tr>
<td>MAFA</td>
<td>MAF bZIPtranscription factor A</td>
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<tr>
<td>FOXO1</td>
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<tr>
<td>GRP-78</td>
<td>Binding immunoglobulin protein</td>
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<tr>
<td>PERK</td>
<td>Protein kinase R (PKR)-like endoplasmic reticulum kinase</td>
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<tr>
<td>IRE1α</td>
<td>Inositol-requiring enzyme 1 α</td>
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1. Introduction

Diabetic prevalences are continuously increasing and they were predicted to reach 693 million in 2045[1]. Various factors contributed to the emergence of diabetes ranging from parental genetics [2], maternal epigenetic inheritance due to nutritional imbalances consumption during pregnancy [3], lifestyle, and diet [4, 5]. Physiologically, diabetes could be due to insulin resistance [6], insulin secretory dysfunction [7], or death of pancreas β-cell [8]. The pathogenesis of Type 2 diabetes mellitus (T2D) related to obesity has been well reviewed [6]. Epidemic and epigenetics
that convey relationship between genetics and environment are closely related to T2D cases [9, 10].

The fact that famines impact on the family health, pregnancy planning, lifestyle, and diet in early stages of pregnancy contributed to future risks of various metabolic disorders, such as obesity and diabetes. This fact has been well-reviewed in the literature [9]. Various environmental factors previously mentioned lead to various epigenetic modifications and cause early insulin resistance associated with the fetal low birth weight [10].

Certain patterns of diets increase the chances of T2D due to alteration in the gene expression. High-fat diet is the most commonly studied and frequently used to induce diabetes [11, 12]. High-fat diets internalize and reduce the expression of pancreatic glucose transporter gene (GLUT2) and glucokinase caused by the hyperglycemia and create a vicious loop of impaired insulin secretion [13, 14]. This diet also reduces the expression of GLUT4 protein and causes insulin resistance in skeletal muscles. High-fat diets also inactivated insulin receptor substrate (IRS-1) in liver and caused inflammation in mice models [15]. Methylation studies on PDK4 also revealed that high-fat-diet-induced methylation on a specific CpG site before the onset of hyperglycemia as one proof of epigenetic regulation plays an important role in metabolic disorder [16].

Primary food with high glycemic index, such as rice, is a staple food for more than half of the world’s population in various Asian countries [17]. High carbohydrate diet, such as refined grain is also associated with an increased risk of T2D [18-20]. High sucrose and fructose diets are also contributing factors to T2D since sucrose and fructose cause pancreas and liver toxicity [21-23]. Another relevant Asian food additive that can induce T2D is the high intake of MSG [24-28]. Epigenetically, a newborn female in the suckling period who eats a high-carbohydrate diet has been reported to readily develop hyperinsulinemia and to acquire obesity in the adulthood [29]. The second generation of these female rats spontaneously develop the similar phenotype even without any intervention studies indicating maternal fetal programming [29]. MSG-induced obesity by subcutaneous injection of female Wistar rats’ parent, has been reported to bring forth male offspring that experienced various metabolic disorders, such as insulin and leptin resistance [30]. These initial facts implied that both high-carbohydrate and high-MSG diets contribute to the emergence of T2D.

To the extent of the authors’ literature reviews, diets with high carbohydrate and high MSG have not been so extensively reviewed as those with high fat (especially in the consequences of
high-carbohydrate and high-MSG intakes on gene expression). This review focuses on exploring the genetic interactions of both diet patterns that leads to T2D. Literature reviews related to T2D and human central metabolism were employed to initially screen some genes or proteins that have been extensively studied. Then, the possibilities of alteration of these genetic expressions using carbohydrate and MSG adjustment were also investigated. Thus, this review can provide insights into the screening processes of genes that can serve as potential biomarkers in T2D prediction. The genes or the proteins can also offer possible breakthroughs in therapies for T2D patients.

2. Genetic Aspects that Promote T2D: High-Carbohydrate Diet Study

High-carbohydrate feeding after a period of time of non-carbohydrate diets caused the mice to enter fast hyperglycemic period [13]. The high-carbohydrate diet in mice models dephosphorylate FoxO1 without reducing its expression where the phosphorylation was regulated in Akt pathway. Thus, FoxO1 stayed in the nucleus and significantly reduced the expression of $PDX1$, $NKX6.1$, and $MAFA$ genes that are essential for the survival and the maintenance of $\beta$-pancreas cell and insulin production [13, 31, 32]. High-fructose diets were also found to increase both the m-RNA content of FoxO1 and the expression of pancreatic $GRP-78$, $PERK$, $IRE1\alpha$, $XBP1$, $CHOP$ gene, hepatic $GRP-78$, and caspase activity [21]. All these genes belong to the family of endoplasmic reticulum stress markers and relate to cell death. Interestingly, high fructose diets also reduce the expression of $INSIG1$[21]. This is the protein that regulates $SREBP-1c$ that is important to synthesize fat when the cells are rich in carbohydrate [33]. In contrast, activation and retention of FoxO1 in the nucleus by deacetylation are essential to protect $\beta$-pancreas cell of diabetic mice within the long term by reducing the dependence on fatty acid oxidation as energy source [34]. This signifies that FoxO1 activation might be one approach of our body to control homeostasis.

Animal models showed that high-carbohydrate diet induced the expression of hepatic acetyl-CoA carboxylase stearoyl-CoA desaturase 1 gene ($Scd1$), while $Scd1$ normally is not expressed in liver but expressed constitutively in adipose tissue [35–38]. High-carbohydrate diet was found to increase the expression of various elongase and desaturase enzymes that synthesize unsaturated fatty acid, especially mono-unsaturated fatty acid (MUFA) in liver [39]. $Scd1$ activation created vicious cycle which created insulin resistance. Down-regulation of $Scd1$ proved to increase the phosphorylation of AKT and to alleviate the insulin resistance [40–43].
Although Scd1 might be an interesting gene to be downregulated, Scd1 deficiency alone was found to be insufficient to protect mice from getting obese [44]. In contrast, the activation of Scd1 gene specifically in skeletal muscle enhanced the activation of PPAR-δ to oxidize fat and increased the metabolism in skeletal muscles that could protect T2D mice from obesity [45]. This opposing phenotype in skeletal muscles and hepatic cells both arising from the activation of Scd1 expression denoted that each protein behaves differently and possibly targets different proteins in each organ. The Scd1 gene correlation with high-carbohydrate diet has been investigated for more than two decades but with no firm consequences. Care must be taken when making a research to silence this gene or to make an inhibitor for Scd1. Clearly, more data are needed to be able to map the effect of Scd1 on not only various genes but also various organs.

ATF4 (or CREB2) deficiency has been shown to suppress the expression of SCD1 in liver, and ATF4-deficiency mice has lower fat content compared to the normal genotype. In high-carbohydrate diet mice, deletion of ATF4 improved insulin sensitivity and caused hypoglycemia [46, 47]. ATF4 deletion also significantly reduced the expression of hepatic PPAR-γ which contributed to lipogenesis resulting in reduction of other genes expression involved in lipogenesis, such as SREBP-1c and acetyl-coA carboxylase. ATF4 deletion also protected high-fructose diet mice from developing hypertriglyceridemia and liver steatosis [48]. This fact was further enhanced by the downregulation of ATF4 in liver by miRNA-214 that could alleviate gluconeogenesis and reduce the expression of FoxO1 in high-fat diet mice [49]. MEG3, a non-coding RNA, was found to be a competing endogenous RNA (ceRNA) for miRNA-214 that resulted in increase of ATF4 and FoxO1 expressions that create insulin resistance [50]. These facts might seem that downregulating ATF4 or regulating the miRNA214-MEG3 axis can be a promising way to combat T2D. Nevertheless, referring to the contrasting long-term effect of FoxO1 [34], more data are required to observe long-term effects of ATF4 up- or down-regulation on the diabetic animal models.

Evenly, nutritional factors of high-carbohydrate and high-fat diet induced diabetic mice overlap with each other in the genetic pathways when a different metabolic pathway is used. This condition possibly occurs when food enters the body and several mechanisms of metabolisms interact with each other to form a complex mechanism to maintain homeostasis. Prolonged imbalanced diet or excessive carbohydrate consumption may lead to pathophysiology of T2D. The idea of some gene expression and protein activity alterations when the body encounters high-carbohydrate diet is summarized in the following Figure 1.
FIGURE 1. Mechanism of high-carbohydrate and high-fructose diets affecting gene expression and protein activity.

3. Genetic Aspects that Promote T2D: High-MSG Intervention Study

Monosodium glutamate has been linked with various metabolic disorders. Metabolism of MSG by dietary intake is well reviewed [51]. Glutamate is a non-essential amino acid that is usually oxidized or acted as precursor for other amino acids in gut. With excess of MSG intakes, the intestine capacity to absorb MSG remain unchanged. In neonatal primate, high dose of MSG administered by gastric tube, induced elevation of glutamate and aspartate content (the result of glutamate metabolism by liver) after one or two hours of treatment without any lesion in neuron [52]. Thus, MSG is considered as GRAS food additive.

Here, the focus of the study is the genetical and experimental effects of MSG intervention study towards expression of genes and metabolism. However, it should be taken into account that various experimental data used MSG injection to develop obesity and hyperglycemic animal models to reveal the genetic architecture between MSG and T2D. MSG is also now a suspected obesogen - a small chemical that could disrupt fat metabolism and appetite [53]. MSG was found to impair glucagon-like peptide (GLP-1) secretion in cell model, a peptide hormone that is important for β-cell growth and insulin production [54]. In short term (3h), secretion of GLP-1...
was increased, but in chronic term (72h), cytotoxicity was observed and there was a reduction in GLP-1 secretion [55].

MSG-induced hyperglycemia caused the same insulin resistance phenomenon induced by streptozotocin. MSG also caused obesity in the non-genetic mice models. However, MSG-induced diabetic mice did not experience an increase in expression of TNF-α, a marker that is usually used to indicate obesity and might also cause diabetes [56, 57]. No reduction of pancreatic β-cell in the MSG-induced diabetes was observed compared to that in the streptozotocin-induced diabetes [25].

MSG-induced diabetic mice exerted decreased content of GLUT4 protein (not GLUT1), disrupt glucose utilization, and caused insulin resistance [58]. This is due to methylation of Slc2a4 promoter area that produced GLUT4 by H3K9me3 using gastrocnemius skeletal cell [59]. An increase of Slc2a2 gene expression (encoding GLUT2) and pck1 (encoding key enzyme in gluconeogenesis in the liver) was also induced in MSG-diabetic mice. This increase caused glucose outflow and created hyperglycemia [60].

MSG-induced diabetes also takes a longer time to develop hyperglycemia phenomenon, and the obesity period is usually the first indicator [61, 62, 26, 63]. Subcutaneous injection of rats with MSG reduced the expression of genes related to the fat oxidation, such as PPARα, ACO, CPT1, and BIFEZ [64, 65]. Conversely, MSG-induced diabetic mice in neonatal period gain an increase of expression in PPARα and PPARγ, and inflammation [66]. Although both mechanisms are intertwined, MSG observably induced the lipogenesis. Chiglitazar, the agonist PPARα and PPARγ, is reported to inhibit the phosphorylation of PPARγ, thus deactivates the protein and increases the expression of ANGPTL4 and PDK4[67–69]. ANGPTL4 is a protein that protects human from getting obese and myocardial infarction due to high-fat diet by inhibiting the lipoprotein lipase activity, reducing free fatty acid levels in serum [70]. PDK4 is an enzyme that turns off the pyruvate dehydrogenase and in turn, activates the β-oxidation pathway that is often expressed in skeletal muscle cell and can be repressed by insulin. An increase of PDK4 expression is often observed in diabetic patients and increases insulin resistance and dependence on fatty acids oxidation as energy source [71, 72]. However, in a short-term high-fat diet, the increase of PDK4 expression is important to balance the glucose and fat level. The increase of ANGPTL4 and PDK4 expression is regarded as the feedback mechanism to protect cells from fatty acid-induced oxidative stress [73, 74].
The loss of function experiment using skeletal muscle cells and adipocytes on TIF2 revealed PPARγ expression reduction [75]. The deletion of TIF2 reduced the expression of lipoprotein lipase, aP2, and increased lipolysis and the resistance of MSG-diabetic induced mice from getting obese in combination with SRC1 expression for better energy expenditure [75]. Experiment on TIF2\(-/\) mouse supported the idea about the role of TIF2 on obesity whereas TIF2 and SRC1 act antagonistically towards UCP3 expression [76]. Silencing TIF2 gene increased the expression of UCP3 and in turn, increased body metabolism and reduced weight gain [77]. Loss-of-function of TIF2 also induced the expression of PGC-1α in skeletal muscle cells, and the expression increased the oxidative metabolism of muscle cell [76, 78]. SRC3 deletion on mice also increased the PGC-1α activity by reducing acetylation on skeletal muscle cells [79]. However, expressed PGC-1α raised different phenotypes from different organs and periods of induction. Pancreatic overexpression of PGC-1α in neonatal period inhibited the expression of PDX1. The inhibition of PDX1 expression caused dysfunction and mass reduction in pancreatic β-cell. However, PGC-1α overexpression in the adult mice did not affect the pancreatic β-cell [80].

Recently, SIRT1, a histone deacetylase protein, has been proved to increase insulin sensitivity. SIRT1 expression improved glycemic control and insulin sensitivity on liver, muscle, adipose tissue and β-cell pancreas [81, 82]. It is further supported by mice that are deficient in SIRT1 which develop hyperglycemic and insulin resistance [83]. MSG-induced diabetic mice does not seem to cause any changes in SIRT1 expression level. However, various ligands that acted as SIRT1 activator such as resveratrol, SRT1720, and MHY2233, improved the steatosis condition.
[60, 84, 85]. In contrast, Genetic diabetic db/db mice reportedly were in use [86]. Although the activation of SIRT1 did stimulate the pancreatic β-cell plasma insulin concentration, SIRT1 activation caused a reduction in body temperature and metabolism (torpor condition) with more long-term effects of weight gain and hepatic steatosis [86].

However, acute knockout of SIRT1 lead to reduction of hyperglycemia setting and an increase of insulin sensitivity by increasing the liver responsiveness to insulin and reducing gluconeogenesis [87, 88]. The results regarding SIRT1 effects on gluconeogenesis and insulin sensitivity seem inconsistent. This discrepancy could be due to the feedback mechanism on the SIRT1-FOXO1 pathway by SHP (encoded by Nr0b2) [89]. Furthermore, SIRT1 knockout in healthy mice brings normal fed and fasting blood glucose level [89]. However, SIRT1 knockout in genetic diabetic mice (double knockout on IRS1/2) resulted in better blood glucose level and glucose tolerance, although the mice were still insulin resistant. This implied that SIRT1 activation can be completed in genetically derived diabetic patients or in already diabetic patients. SIRT1 treatment might not be used to prevent people from diabetes.

In general, MSG-induced mice are more related to obese phenomenon. Quite a few involved genes are intertwined with obesity, such as fat metabolism from PPARs family. While high-carbohydrate-induced diabetes can also cause lipogenesis by balancing the excess of carbohydrate into fat, MSG-induced diabetes seems to directly activate lipogenesis. The changes in genes expression triggered by MSG-induced T2D are summarized in Figure 3.
FIGURE 3. Mechanisms of changing genes expression affected by MSG-induced diabetes and of genes affecting MSG-induced diabetes
4. Involvement of Genes and Proteins in T2D

It is important to figure out whether the disruption of the gene expression is the reason for the T2D, or whether the disruption is generated by the T2D. Two categories were used to sort some genes whether the genes induce T2D, or T2D changes the genes expression (Table 1). The genes that could affect T2D development might be used as diabetes markers and targeted to prevent T2D. While some gene expressions that are altered after T2D has occurred can be treated to alleviate the diabetes symptoms. The delicate interaction of the proteins, such as pleiotropic effects and highly branched signaling pathways and feedback mechanisms, also complicates the treatment of the targeted gene without disrupting the homeostasis of our body. Genes or proteins whose activities are altered after diabetes and increase diabetes severity, or the further missing link that still has to be developed is placed in not determined (N.D).

### TABLE 1. Summary of genes involved in diet-induced diabetes

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<td>High-MSG</td>
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<td>Increase of the content and collaboration with non-alcoholic steatohepatitis to facilitate the glucose input to hepatocyte</td>
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<td>Lowered expression might cause obesity</td>
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<td>CPT1 [gene]</td>
<td>Increase of expression level possibly leading to obesity</td>
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<td>✓ [97]</td>
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<td>Increase of muscle PDK4 expression</td>
<td>Changed by T2D</td>
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<td>Activation at neonatal period reduced PDX1 expression and pancreas maturation</td>
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<td>SIRT1 [gene]</td>
<td>Increase of this gene expression alleviates symptoms in the already diabetic patient</td>
<td>✓</td>
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Various genes such as FOXO1, PDX1, ATF4, and INSIG1 proved to be important for the development of β-pancreas cells, or to maintain the balance of metabolism to increase glucose tolerance. Meanwhile, genes expression alteration that directly corelate with carbohydrate or fat metabolism, such as GLUT families, pck1, scd1, and PPAR are more likely caused by feedback mechanism and complex regulation to give better glucose level performa [60, 97]. Disturbance of expression in genes like ACO, CPT1, TIF2, SRC1, scd1 and UCP3 in muscle cells and adipocyte cells are more into causing obesity, in which these genes are related to fat metabolism and energy expenditure. Caution must be taken that diabetes could also abberated these genes expression directly related to metabolism and disruption of these genes in early stage of development could also cause various physiological imbalances. However, genes like TIF2, SRC1, and PGC-1α were predicted to be more upstream in the signaling pathway. Thus, modulation of these genes might prevent further physiological abberations related to metabolism imbalances such as obesity and diabetes. SIRT1 expression was not changed by diabetes and its knockout also did not cause T2D. SIRT1 is a promising gene to be targeted in the already diabetic patient as previously stated above. We further hypothesized that based on the animal studies, both highcarbohydrate (found in high glycemic index food or energy-dense food) and introduction of high MSG (by injection) might reinforce each other to increase the prevalence of T2D or other metabolic disorders. The possibility of intervention study employing both factors might be noteworthy to be investigated.
5. Population-based Studies of High-carbohydrate and High-MSG Diet

Using animal and cell line models, high-MSG and high-carbohydrate diets correlated and might also contribute to the onset of T2D by disrupting expression and the activity of various genes mentioned in Table 1. However, studies on epidemiology might support or contrast the idea of the correlation between T2D and high-MSG or high-carbohydrate diet. Various factors contributed to this conditions such as age, ethnicity, genetics, anatomical and metabolic differences, or socioeconomics or even in the experimental design itself [100].

Population study of dietary carbohydrate intake above normal level in Japanese population showed that obese participants develops T2D more readily than non-obese participants. This indicated that large samples, genetic effects, participants’ backgrounds should be considered in the epidemiology study [101]. However, epidemiological studies in China, India, United States, and UAE supported the dietary style of high-carbohydrate intake (such as refined grain and added sugar) positively correlated with T2D [18, 102–105]. Another profound study on epidemiology related to the increasing risk of T2D was conducted on sugar-sweetened diet beverages in female US nurses in 1989 [106]. The intake of these high-calorie beverages (such as, soft drink and fruit punch) was said to be associated with the increasing chances of T2D development. More than 60 % diabetic people live in China and India, followed by Japan [103, 107]. Asian countries, such as China, India or UAE are predicted to yield a higher rate of diabetic prevalence [18, 102–105]. Although general population in Japan consume white rice and MSG-enriched food like people in other Asian countries, uniquely, Japan is projected to have only a small increase in the ratio of its diabetic people in 2025. This fact might be due to the nationwide health guidance and lifestyle intervention program [107–109].

While studies on epidemiology related to high-carbohydrate diet related to the risk of T2D development are clearly [18, 102–105], findings about human population study at risk of high-MSG diet are inconsistent. Studies on MSG-related diabetic cases have been frequently reported using animal models. There is a lack of epidemiological data of MSG consumption which contribute to T2D in comparison to those of high-carbohydrate consumption. Epidemiology in Spanish population has been linked to the increasing risks of getting T2D to cardiovascular diseases due to high glutamate plasma level [110]. Based on another epidemiology in Thailand, daily consumption exceeding 5 g of MSG is considered risky to carry metabolic disorders,
including T2D [111]. MSG intakes have also been reported to increase the incidence of overweight [112]. However, two studies from the Jiangsu Nutrition Study argued that MSG intake did not correlate with obesity, and even high MSG intake was negatively associated with hyperglycemia [113, 114].

One possible explanation that could explain the opposing results among the studies of epidemiology is the unready transportation from the intestine into the blood circulation in contrast to various experimental data that used MSG-induced diabetic mice models by MSG subcutaneous injection [51, 115]. Another explanation arises from experimental data where life period is an important factor related to the genetic programming by environmental factors. Mice at the age of 4 months old with high-MSG diet are prone to various metabolic disorders, including the increased signs of glucose intolerance. However, along with the aging process, the impairment of metabolism from the obesity effects can be attenuated [116].

By considering both experimental data from animal or cell culture studies with epidemiological data, we summarize that high-carbohydrate diet evidently positively correlates with T2D and could cause the onset of T2D. Although MSG studies are still in conflict with one another, we do not encourage people to slacken their diets by consuming high amount of MSG based on the experimental data of MSG potentials to alter homeostasis on carbohydrate and fat metabolism. All in all, lifestyle intervention shows to be a promising primary prevention of diabetes, and healthy lifestyle is shown to be comparable with metformin intake as reported by Indian Diabetes Prevention Programme [104]. Govermental policies can play a huge role on combating the increasing prevalence of diabetes by encouraging a healthy diet and lifestyle, such as taxation program in Thailand for beverages which contain high level of sugar content [117].

6. Conclusion and Future Perspectives

High-fat diet is commonly known to induce T2D, especially in the case of high-carbohydrate and high-MSG diets. However, high-MSG diet requires longer time to develop hyperglycemia preceded by obesity. Various genes, especially genes related to glucose and fat metabolism are interrelated within these two diets. Branched signal transduction pathways and different phenotypes of each gene in different organs or ages revealed complicated mechanisms that should be taken as precautions as the targeted gene of interest to treat T2D or to construct a specific biomarker for T2D. Initially, some activated or repressed genes are only a feedback
mechanism to control body homeostasis related to the imbalanced diet. For example, high-carbohydrate diet increased SCD-1 expression. Prolonged feedback mechanism often creates vicious cycle thus developing metabolic syndromes including obesity and T2D.

Increasing FoxO1 and ATF4 expressions or their activation in high-carbohydrate-induced diabetic mice will lead to insulin resistance. It could be interesting to study the repression or the side effects of both genes of diabetic mice for long-term experiments. Both genes might have potential uses as a biomarker for early detection of the T2D. The fact of MSG-induced diabetic mice often leads to the increase of gene expressions related to lipogenesis, such as PPARs family. However, the changes in PPARs expression and activation may disrupt the balance between glucose and lipid metabolism. Both TIF2 and SIRT1 are promising genes in alleviating insulin resistance developed from MSG-induced diabetes. However, these strategies have also exhibited some drawbacks. TIF2 silencing increased the expression of PGC-1α that inhibited the maturation of pancreas at neonatal period. Further information on TIF2 silencing of pancreatic cells from various ages of mice models may enlighten the benefits of targeting TIF2 as a gene of interest to treating T2D. It is still unclear how the MSG affects the TIF2 expression in β-cells. Similarly, SIRT1 is indeed an interesting target gene, however, precautions should be taken in drug administration, diet lifestyle, and targeted organs. Otherwise, the disruption of the delicate balance of homeostasis may lead to worsening physical conditions. Studying the SIRT1 signal transduction pathway and its effects on T2D in a more long-term experiment will shed more understanding into how SIRT1 maintains homeostasis.

Acknowledgments

The research and writing of this paper was funded by Indonesia Ministry of Research, Technology, and Higher Education (021/SP-Lit/LPPM-01/DRPM/Multi/FTB/III/2019). We thank Helen Hendaria Kamandhari, Ph.D. for her editing and comments.

Conflict of interests: All authors have declared that no conflict of interests exists.

Ethical approval: The studies conducted in this article do not involve human participants or animals.

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Expression of Peroxisome Proliferator-Activated Receptors in Mice. Basic & Clinical Pharmacology & Toxicology, 108(6), 406–413.


Wang, R. H., Kim, H. S., Xiao, C., Xu, X., Gavrilova, O., & Deng, C. X. (2011). Hepatic Sirt1 deficiency in mice impairs mTorc2/Akt signaling and results in hyperglycemia, oxidative damage, and insulin resistance. The Journal of Clinical Investigation, 121(11), 4477-4490.


When revising your work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.

Your revision is due by 25 Feb 2020.

You will see a menu item called 'Submissions Needing Revision'. You will find your submission record there.

Please make sure to submit your editable source files (i.e. Word, tex).

Yours sincerely,
Sebastiano Filetti
Editor-in-Chief
Endocrine

COMMENTS FOR THE AUTHOR:

Reviewer #1: 1- MSG (monosodium glutamate) as an abbreviation should be spelled out in the title as well as the abstract and should be added into the abbreviation list. Moreover, MSG should be spelled out when it is first mentioned then only MSG and not monosodium glutamate should be used later. This should be done for all the used abbreviations.

Reply: MSG and T2D in the title, and abstract have been prolonged for the first time However, for the gene name, we still use the abbreviations.

2- The manuscript should be revised for linguistic and grammatical mistakes as well as typographical errors e.g. the authors (in the abstract), dephosphorilation of FoxO1 (in Figure 1) and in page 5 line 119 "Scd1 deficient alone …" should be "Scd1 deficiency alone …".

Reply: We are grateful for the input. We change the figure 1 also ask Mrs Helen to recheck and do some proofread on the manuscript.

3- The authors stated that high carbohydrate diet plus high intake of MSG contribute to the emergence of type 2 diabetes. The authors should differentiate between correlation and causation. The authors should show which studies revealed only that the prevalence of type 2 diabetes is correlated with high carbohydrate diet and high intake of MSG and which studies investigated the possibility that high carbohydrate diet and high intake of MSG could lead to type 2 diabetes.

Reply: we deleted the sentence “both factors combine to increase risk of T2D” in the introduction. We noticed that we have to tone down this sentence. Therefore, we just put this as hypothesis that might be interesting to be investigated in animal studies in the last paragraph in the genetic aspects section (before entering human population study).

For genetic aspects, such as in Table 1, we already wrote that for genes which affects T2D development, it is highly probable that disruption of those genes by imbalance diet could lead to the onset of hyperglycemia. As for changed by T2D, then the hyperglycemic period happen first that lead to the change to gene expression. However, indeed many genes are still on the side of N.D., which is the there is missing link on the time period of the activation of the phenotypes. Meanwhile, it can be also caused by a feedback loop from the activation / suppression of the genes itself that create vicious cycle. Also to give balance to the
experimental data, we then added a new section about human-population study. This will describe more about the correlation between lifestyle and diet to the metabolic disorders. We also added several sentences in the MSG section and in the epidemiology studies that highlighted the main difference in the treatment for MSG case, in which in various animal, genetic, and experimental studies, the model was created by MSG injection, and not by feeding.

4- Are there any studies showing non-significant correlation between the prevalence of type 2 diabetes is and high carbohydrate diet as well as high intake of MSG? You should show all relevant studies!!

Reply: We added some results from epigenetic studies related to the onset of T2D due to high-carbohydrate and high-MSG diet. We also added a new section related to a more comprehensive epidemiological data so that the experimental data can be compared with population-based study and gave a bigger picture of the status quo on both high-carbo and high-MSG. Indeed, despite various factors plays in the epidemiological study, major results for high-carbohydrate diet is positively correlated with diabetes and could also give rise to diabetes for a healthy patient. But for high-MSG diet, many results are in conflict with each other. We also tried to give some explanation to this in the new section and also in the first paragraph of the impact of MSG by describing the fate of MSG in the gut and why MSG can be considered GRAS as food additive.

5- It would be great if the authors can explain the strategy they used to pick up the genes to be discussed in this review.

Reply: New sentences are added in the last paragraph of the introduction to explain basic ideas on how we screen some genes and gather the articles to assign the review.

6- I suggest adding a small paragraph about the fate (absorption and metabolism) of MSG after its ingestion.

Reply: A new paragraph is added in the impact of MSG section as its first paragraph (line 173-179). There, we describe how MSG can be considered GRAS as food additive We also added a new paragraph after the section to differentiate that various genetic and experimental data employed either MSG injection (subcutan or peritoneal) or by cell culture not by feeding.

7- The authors should also mention epigenetic mechanism leading to insulin resistance by referring to: J Hypertens. 2019;37(11):2123-2134. doi:10.1097/HJH.0000000000002156. Is something known about epigenetic mechanisms of High-Carbohydrate and High-MSG Diet induced insulin resistance?

Reply: Epigenetic experimental data have been added in the introduction, such as famine, related to low birth weight, imbalance diet, fetal programming by impaired maternal.

8- In Figure 3, what is the relation between the factors in the upper part of the figure and the term "MSG induced".

Reply: it has been corrected to

9- The authors should spell out MSG in the title. In general, use rather full names then abbreviations.

Reply: It is corrected.
High MSG Diet

neonatal periode

Increase PPAR γ, PPAR α expression

Lipogenesis

Obesity
The genetic basis of high-carbohydrate and high-monosodium glutamate diet related to the increase of likelihood of type 2 diabetes mellitus: a review

Joshua Nathanael1 · Hans Cristian Adhinatya Harsono1 · Aubrey Druce Wibawa1 · Putu Suardana1 · Yoanes Maria Vianney1 · Sulistyo Emantoko Dwi Putra1

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Abstract

Diabetes is one of the most common metabolic diseases. Aside from the genetic factor, previous studies stated that other factors such as environment, lifestyle, and paternal–maternal condition play critical roles in diabetes through DNA methylation in specific areas of the genome. One of diabetic cases is caused by insulin resistance and changing the homeostasis of blood glucose control so glucose concentration stood beyond normal rate (hyperglycemia). High fat diet has been frequently studied and linked to triggering diabetes. However, most Asians consume rice (or food with high carbohydrate) and food with monosodium glutamate (MSG). This habit could lead to pathophysiology of type 2 diabetes mellitus (T2D). Previous studies showed that high-carbohydrate or high-MSG diet could change gene expression or modify protein activity in body metabolism. This imbalanced metabolism can lead to pleiotropic effects of diabetes mellitus. In this study, the authors have attempted to relate various changes in genes expression or protein activity to the high-carbohydrate and high-MSG-induced diabetes. The authors have also tried to relate several genes that contribute to pathophysiology of T2D and proposed several ideas of genes as markers and target for curing people with T2D. These are done by investigating altered activities of various genes that cause or are caused by diabetes. These genes are selected based on their roles in pathophysiology of T2D.

Keywords

High carbohydrate · Insulin resistance · Monosodium glutamate · Obesity · Type 2 diabetes mellitus

Abbreviations

GLUT4 Glucose transporter 4
PDX1 Pancreatic and duodenal homeobox 1
NKX6.1 NK6 homeobox 1
MAFA MAF bZIP transcription factor A
FOXO1 Forkhead box protein O1
GRP-78 Binding immunoglobulin protein
PERK Protein kinase R (PKR)-like endoplasmic reticulum kinase
IRE1α Inositol-requiring enzyme 1 α
XBP1 X-box binding protein 1
CHOP C/EBP homologous protein
INSIG1 Insulin induced gene 1
SREBP-1c Sterol regulatory element binding protein 1c
SIRT1 NAD-dependent deacetylase sirtuin-1
SCD1 Stearoyl-CoA desaturase-1
PPAR Peroxisome proliferator-activated receptor
ATF4 Activating transcription factor 4
CREB-2 cAMP-response element binding protein 2
MEG3 Maternally expressed 3
SLC2A4 Solute carrier family 2 member 4
H3K9me3 Trimethylation of lysine 9 on histone H3 protein
PCK1 Phosphoenolpyruvate carboxykinase 1 (soluble)
ACO Acyl-CoA oxidase
CPT1 Carnitine palmitoyltransferase 1
BIF EZ Bifunctional enzyme
ANGPTL4 Angiopoietin-like 4
PDK4 Pyruvate dehydrogenase lipoamide kinase isozyme 4
TIF2 Transcriptional mediators/intermediary factor 2
UCP3 Mitochondrial uncoupling protein 3

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1 Department of Biology, Faculty of Biotechnology, University of Surabaya, Raya Kalirungkut, Surabaya, East Java 60292, Indonesia

Published online: 14 March 2020
Introduction

Diabetic prevalences are continuously increasing and they were predicted to reach 693 million in 2045 [1]. Various factors contributed to the emergence of diabetes ranging from parental genetics [2], maternal epigenetic inheritance due to nutritional imbalances consumption during pregnancy [3], lifestyle, and diet [4, 5]. Physiologically, diabetes could be due to insulin resistance [6], insulin secretory dysfunction [7], or death of pancreas β-cell [8]. The pathogenesis of type 2 diabetes mellitus (T2D) related to obesity has been well reviewed [6]. Epidemic and epigenetics that convey relationship between genetics and environment are closely related to T2D cases [9, 10]. The fact that famines impact on the family health, pregnancy planning, lifestyle, and diet in early stages of pregnancy contributed to future risks of various metabolic disorders, such as obesity and diabetes. This fact has been well-reviewed in the literature [9]. Various environmental factors previously mentioned lead to various epigenetic modifications and cause early insulin resistance associated with the fetal low birth weight [10].

Certain patterns of diets increase the chances of T2D due to alteration in the gene expression. High-fat diet is the most commonly studied and frequently used to induce diabetes [11, 12]. High-fat diets internalize and reduce the expression of pancreatic glucose transporter gene (GLUT2) and glucokinase caused by the hyperglycemia and create a vicious loop of impaired insulin secretion [13, 14]. This diet also reduces the expression of GLUT4 protein and causes insulin resistance in skeletal muscles. High-fat diets also inactivated insulin receptor substrate (IRS-1) in liver and caused inflammation in mice models [15]. Methylation studies on PDK4 also revealed that high-fat-diet-induced methylation on a specific CpG site before the onset of hyperglycemia as one proof of epigenetic regulation plays an important role in metabolic disorder [16].

Primary food with high glycemic index, such as rice, is a staple food for more than half of the world’s population in various Asian countries [17]. High carbohydrate diet, such as refined grain is also associated with an increased risk of T2D [18–20]. High sucrose and fructose diets are also contributing factors to T2D since sucrose and fructose cause pancreas and liver toxicity [21–23]. Another relevant Asian food additive that can induce T2D is the high intake of MSG [24–28]. Epigenetically, a newborn female in the suckling period who eats a high-carbohydrate diet has been reported to readily develop hyperinsulinemia and to acquire obesity in the adulthood [29]. The second generation of these female rats spontaneously develop the similar phenotype even without any intervention studies indicating maternal fetal programming [29]. MSG-induced obesity by subcutaneous injection of female Wistar rats’ parent, has been reported to bring forth male offspring that experienced various metabolic disorders, such as insulin and leptin resistance [30]. These initial facts implied that both high-carbohydrate and high-MSG diets contribute to the emergence of T2D.

To the extent of the authors’ literature reviews, diets with high carbohydrate and high MSG have not been so extensively reviewed as those with high fat (especially in the consequences of high-carbohydrate and high-MSG intakes on gene expression). This review focuses on exploring the genetic interactions of both diet patterns that leads to T2D. Literature reviews related to T2D and human central metabolism were employed to initially screen some genes or proteins that have been extensively studied. Then, the possibilities of alteration of these genetic expressions using carbohydrate and MSG adjustment were also investigated. Thus, this review can provide insights into the screening processes of genes that can serve as potential biomarkers in T2D prediction. The genes or the proteins can also offer possible breakthroughs in therapies for T2D patients.

Genetic aspects that promote T2D: high-carbohydrate diet study

High-carbohydrate feeding after a period of time of non-carbohydrate diets caused the mice to enter fast hyperglycemic period [13]. The high-carbohydrate diet in mice models dephosphorylate FoxO1 without reducing its expression where the phosphorylation was regulated in Akt pathway. Thus, FoxO1 stayed in the nucleus and significantly reduced the expression of PDX1, NKX6.1, and MAFA genes that are essential for the survival and the maintenance of β-pancreas cell and insulin production [13, 31, 32]. High-fructose diets were also found to increase both the m-RNA content of FoxO1 and the expression of pancreatic GRP-78, PERK, IRE1α, XBP1, CHOP gene, hepatic GRP-78, and caspase activity [21]. All these genes belong to the family of endoplasmic reticulum stress markers and relate to cell death. Interestingly, high fructose diets also reduce the expression of INSIG1 [21]. This is the protein that regulates SREBP-1c that is important to synthesize fat when the cells are rich in carbohydrate [33]. In contrast, activation and retention of FoxO1 in the nucleus by deacetylation are essential to protect β-pancreas...
cell of diabetic mice within the long term by reducing the dependence on fatty acid oxidation as energy source [34]. This signifies that FoxO1 activation might be one approach of our body to control homeostasis.

Animal models showed that high-carbohydrate diet induced the expression of hepatic acetyl-CoA carboxylase stearoyl-CoA desaturase 1 gene (Scd1), while Scd1 normally is not expressed in liver but expressed constitutively in adipose tissue [35–38]. High-carbohydrate diet was found to increase the expression of various elongase and desaturase enzymes that synthesize unsaturated fatty acid, especially monounsaturated fatty acid in liver [39]. Scd1 activation created vicious cycle which created insulin resistance. Downregulation of Scd1 proved to increase the phosphorylation of AKT and to alleviate the insulin resistance [40–43].

Although Scd1 might be an interesting gene to be downregulated, Scd1 deficiency alone was found to be insufficient to protect mice from getting obese [44]. In contrast, the activation of Scd1 gene specifically in skeletal muscle enhanced the activation of PPAR-δ to oxidize fat and increased the metabolism in skeletal muscles that could protect T2D mice from obesity [45]. This opposing phenotype in skeletal muscles and hepatic cells both arising from the activation of Scd1 expression denoted that each protein behaves differently and possibly targets different proteins in each organ. The Scd1 gene correlation with high-carbohydrate diet has been investigated for more than two decades but with no firm consequences. Care must be taken when making a research to silence this gene or to make an inhibitor for Scd1. Clearly, more data are needed to be able to map the effect of Scd1 on not only various genes but also various organs.

ATF4 (or CREB2) deficiency has been shown to suppress the expression of SCD1 in liver, and ATF4-deficiency mice has lower fat content compared with the normal genotype. In high-carbohydrate diet mice, deletion of ATF4 improved insulin sensitivity and caused hypoglycemia [46, 47]. ATF4 deletion also significantly reduced the expression of hepatic PPAR-γ which contributed to lipogenesis resulting in reduction of other genes expression involved in lipogenesis, such as SREBP-1c and acetyl-coA carboxylase. ATF4 deletion also protected high-fructose diet mice from developing hypertriglyceridemia and liver steatosis [48]. This fact was further enhanced by the downregulation of ATF4 in liver by miRNA-214 that could alleviate gluconeogenesis and reduce the expression of FoxO1 in high-fat diet mice [49]. MEG3, a noncoding RNA, was found to be a competing endogenous RNA for miRNA-214 that resulted in increase of ATF4 and FoxO1 expressions that create insulin resistance [50]. These facts might seem that downregulating ATF4 or regulating the miRNA-214-MEG3 axis can be a promising way to combat T2D. Nevertheless, referring to the contrasting long-term effect of FoxO1 [34], more data are required to observe long-term effects of ATF4 up- or downregulation on the diabetic animal models.

Evenly, nutritional factors of high-carbohydrate and high-fat diet-induced diabetic mice overlap with each other in the genetic pathways when a different metabolic pathway is used. This condition possibly occurs when food enters the body and several mechanisms of metabolisms interact with each other to form a complex mechanism to maintain homeostasis. Prolonged imbalanced diet or excessive carbohydrate consumption may lead to pathophysiology of T2D. The idea of some gene expression and protein activity alterations when the body encounters high-carbohydrate diet is summarized in the following Figs. 1 and 2.

**Genetic aspects that promote T2D: high-MSG intervention study**

Monosodium glutamate (MSG) has been linked with various metabolic disorders. Metabolism of MSG by dietary intake is well reviewed [51]. Glutamate is a nonessential amino acid that is usually oxidized or acted as precursor for other amino acids in gut. With excess of MSG intakes, the intestine capacity to absorb MSG remain unchanged. In neonatal primate, high dose of MSG administrated by gastric tube, induced elevation of glutamate, and aspartate content (the result of glutamate metabolism by liver) after 1 or 2 h of treatment without any lesion in neuron [52]. Thus, MSG is considered as GRAS food additive.

Here, the focus of the study is the genetical and experimental effects of MSG intervention study toward expression of genes and metabolism. However, it should be taken into account that various experimental data used MSG injection to develop obesity and hyperglycemic animal models to reveal the genetic architecture between MSG and T2D. MSG is also now a suspected obesogen—a small chemical that could disrupt fat metabolism and appetite [53]. MSG was found to impair glucagon-like peptide (GLP-1) secretion in cell model, a peptide hormone that is important for β-cell growth, and insulin production [54]. In short term (3 h), secretion of GLP-1 was increased, but in chronic term (72 h), cytotoxicity was observed and there was a reduction in GLP-1 secretion [55].

MSG-induced hyperglycemia caused the same insulin resistance phenomenon induced by streptozotocin. MSG also caused obesity in the nongenetic mice models. However, MSG-induced diabetic mice did not experience an increase in expression of TNF-α, a marker that is usually used to indicate obesity and might also cause diabetes [56, 57]. No reduction of pancreatic β-cell in the MSG-induced diabetes was observed compared with that in the streptozotocin-induced diabetes [25].
MSG-induced diabetic mice exerted decreased content of GLUT4 protein (not GLUT1), disrupt glucose utilization, and caused insulin resistance [58]. This is due to methylation of Slc2a4 promoter area that produced GLUT4 by H3K9me3 using gastrocnemius skeletal cell [59]. An increase of Slc2a2 gene expression (encoding GLUT2) and pck1 (encoding key enzyme in gluconeogenesis in the liver) was also induced in MSG-diabetic mice. This increase caused glucose outflow and created hyperglycemia [60].

MSG-induced diabetic mice also takes a longer time to develop hyperglycemia phenomenon, and the obesity period is usually the first indicator [26, 61–63]. Subcutaneous injection of rats with MSG reduced the expression of genes related to the fat oxidation, such as PPARα, ACO, CPT1, and BIFEZ [64, 65]. Conversely, MSG-induced diabetic mice in neonatal period gain an increase of expression in PPARα and PPARγ, and inflammation [66]. Although both mechanisms are intertwined, MSG observably induced the lipogenesis. Chiglitazar, the agonist PPARα and PPARγ, is reported to inhibit the phosphorylation of PPARγ, thus deactivates the protein and increases the expression of ANGPTL4 and PDK4 [67–69]. ANGPTL4 is a protein that protects human from getting obese and myocardial infarction due to high-fat diet by inhibiting the lipoprotein lipase activity, reducing free fatty acid levels in serum [70]. PDK4 is an enzyme that turns off the pyruvate dehydrogenase and in turn, activates the β-oxidation pathway that is often expressed in skeletal muscle cell, and can be repressed by insulin. An increase of PDK4 expression is often observed in diabetic patients and increases insulin resistance and dependence on fatty acids oxidation as energy source [71, 72]. However, in a short-term high-fat diet, the increase of PDK4 expression is important to balance the glucose and fat level. The increase of ANGPTL4 and PDK4 expression is regarded as the feedback mechanism to protect cells from fatty acid-induced oxidative stress [73, 74].

The loss-of-function experiment using skeletal muscle cells and adipocytes on TIF2 revealed PPARγ expression reduction [75]. The deletion of TIF2 reduced the expression of lipoprotein lipase, aP2, and increased lipolysis and the resistance of MSG-diabetic induced mice from getting obese in combination with SRC1 expression for better energy expenditure [75]. Experiment on TIF2−/− mouse supported the idea about the role of TIF2 on obesity whereas TIF2 and SRC1 act antagonistically toward UCP3 expression [76]. Silencing TIF2 gene increased the expression of UCP3 and in turn, increased body
metabolism, and reduced weight gain [77]. Loss-of-function of TIF2 also induced the expression of PGC-1α in skeletal muscle cells, and the expression increased the oxidative metabolism of muscle cell [76, 78]. SRC3 deletion on mice also increased the PGC-1α activity by reducing acetylation on skeletal muscle cells [79]. However, expressed PGC-1α raised different phenotypes from different organs and periods of induction. Pancreatic overexpression of PGC-1α in neonatal period inhibited the expression of PDX1. The inhibition of PDX1 expression caused dysfunction and mass reduction in pancreatic β-cell. However, PGC-1α overexpression in the adult mice did not affect the pancreatic β-cell [80].

Recently, SIRT1, a histone deacetylase protein, has been proved to increase insulin sensitivity. SIRT1 expression improved glycemic control and insulin sensitivity on liver, muscle, adipose tissue, and β-cell pancreas [81, 82]. It is further supported by mice that are deficient in SIRT1 which develop hyperglycemia and insulin resistance [83]. MSG-induced diabetic mice does not seem to cause any changes in SIRT1 expression level. However, various ligands that acted as SIRT1 activator such as resveratrol, SRT1720, and MHY2233, improved the steatosis condition [60, 84, 85]. In contrast, genetic diabetic db/db mice reportedly were in use [86]. Although the activation of SIRT1 did stimulate the pancreatic β-cell plasma insulin concentration, SIRT1 activation caused a reduction in body temperature and metabolism (torpor condition) with more long-term effects of weight gain and hepatic steatosis [86].

However, acute knockout of SIRT1 lead to reduction of hyperglycemia setting and an increase of insulin sensitivity by increasing the liver responsiveness to insulin and reducing gluconeogenesis [87, 88]. The results regarding SIRT1 effects on gluconeogenesis and insulin sensitivity seem inconsistent. This discrepancy may be due to the feedback mechanism on the SIRT1-FOXO1 pathway by SHP (encoded by Nr0b2) [89]. Furthermore, SIRT1 knockout in healthy mice brings normal fed and fasting blood glucose level [89]. However, SIRT1 knockout in genetic diabetic mice (double knockout on IRS1/2) resulted in better blood glucose level and glucose tolerance, although the mice were still insulin resistant. This implied that SIRT1 activation can be completed in genetically derived diabetic patients or in already diabetic patients. SIRT1 treatment might not be used to prevent people from diabetes.

In general, MSG-induced mice are more related to obese phenomenon. Quite a few involved genes are intertwined with obesity, such as fat metabolism from PPARs family. While high-carbohydrate-induced diabetes can also cause lipogenesis by balancing the excess of carbohydrate into fat, MSG-induced diabetes seems to directly activate lipogenesis. The changes in genes expression triggered by MSG-induced T2D are summarized in Fig. 3.

### Involvement of genes and proteins in T2D

It is important to figure out whether the disruption of the gene expression is the reason for the T2D, or whether the disruption is generated by the T2D. Two categories were used to sort some genes whether the genes induce T2D, or T2D changes the genes expression (Table 1). The genes that could affect T2D development might be used as diabetes markers and targeted to prevent T2D. While some gene expressions that are altered after T2D has occurred can be treated to alleviate the diabetes symptoms. The delicate interaction of the proteins, such as pleiotropic effects and highly branched signaling pathways and feedback mechanisms, also complicates the treatment of the targeted gene without disrupting the homeostasis of our body. Genes or proteins whose activities are altered after diabetes and increase diabetes severity, or the further missing link that still has to be developed is placed in not determined (ND).

Various genes such as FOXO1, PDX1, ATF4, and INSIG1 proved to be important for the development of β-pancreas cells, or to maintain the balance of metabolism to increase glucose tolerance. Meanwhile, genes expression alteration that directly corelate with carbohydrate or fat metabolism, such as GLUT families, pck1, scl1, and PPAR are more likely caused by feedback mechanism and complex regulation to give better glucose level performa [60, 97]. Disturbance of expression in genes like ACO, CPT1, TIF2, SRC1, scl1, and UCP3 in muscle cells and adipocyte cells are more into causing obesity, in which these genes are related to fat metabolism and energy expenditure. Caution must be taken that diabetes could also abberated these genes expression directly related to metabolism and disruption of these genes in early stage of development could also cause various physiological imbalances. However, genes like TIF2, SRC1, and PGC-1α were predicted to be more upstream in the signaling pathway. Thus, modulation of these genes might prevent further physiological abberations related to metabolism imbalances such as obesity and diabetes. SIRT1 expression was not changed by diabetes and its knockout also did not cause T2D. SIRT1 is a promising gene to be targeted in the already diabetic patient as previously stated above. We further hypothesized that based on the animal studies, both high carbohydrate (found in high glycemic index food or energy-dense food) and introduction of high MSG (by injection) might reinforce each other to increase the prevalence of T2D or other metabolic disorders. The possibility of intervention study employing both factors might be noteworthy to be investigated.
Population-based studies of high-carbohydrate and high-MSG diet

Using animal and cell line models, high-MSG and high-carbohydrate diets correlated and might also contribute to the onset of T2D by disrupting expression and the activity of various genes mentioned in Table 1. However, studies on epidemiology might support or contrast the idea of the correlation between T2D and high-MSG or high-carbohydrate diet. Various factors contributed to this conditions such as age, ethnicity, genetics, anatomical and metabolic differences, or socioeconomics or even in the experimental design itself [100].

Population study of dietary carbohydrate intake above normal level in Japanese population showed that obese participants develops T2D more readily than nonobese participants. This indicated that large samples, genetic effects, participants’ backgrounds should be considered in the epidemiology study [101]. However, epidemiological studies in China, India, United States, and UAE supported the dietary style of high-carbohydrate intake (such as refined grain and added sugar) positively correlated with T2D [18, 102–105]. Another profound study on epidemiology related to the increasing risk of T2D was conducted on sugar-sweetened diet beverages in female US nurses in 1989 [106]. The intake of these high-calorie beverages (such as, soft drink and fruit punch) was said to be associated with the increasing chances of T2D development. More than 60% diabetic people live in China and India, followed by Japan [103, 107]. Asian countries, such as China, India, or UAE are predicted to yield a higher rate of diabetic prevalence [18, 102–105]. Although general
population in Japan consume white rice and MSG-enriched food like people in other Asian countries, uniquely, Japan is projected to have only a small increase in the ratio of its diabetic people in 2025. This fact might be due to the nationwide health guidance and lifestyle intervention program [107–109].

<table>
<thead>
<tr>
<th>Diet</th>
<th>Gene/protein</th>
<th>Effect</th>
<th>Condition Changed by T2D</th>
<th>Affecting T2D</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>High carbohydrate</td>
<td>FoxO1 [protein]</td>
<td>Dephosphorylated</td>
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<td></td>
<td>Scl1 [gene]</td>
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<td>[48]</td>
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<tr>
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<td>INSI1 [gene]</td>
<td>Reduction of expression</td>
<td>✓</td>
<td></td>
<td>[90]</td>
</tr>
<tr>
<td></td>
<td>FoxO1 [gene]</td>
<td>Increase of expression</td>
<td>✓</td>
<td></td>
<td>[90]</td>
</tr>
<tr>
<td>High-MSG</td>
<td>GLUT4 [protein]</td>
<td>Reduction of expression accompanied with whole-body insulin resistance and increased plasma concentration of inflammatory markers</td>
<td>✓</td>
<td></td>
<td>[91]</td>
</tr>
<tr>
<td></td>
<td>slc2a4 [gene]</td>
<td>Reduction of expression that contributes to the impairment of glycemic homeostasis</td>
<td>✓</td>
<td></td>
<td>[92]</td>
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<tr>
<td></td>
<td>Slc2a2 [gene]</td>
<td>Increase of the content and collaboration with nonalcoholic steatohepatitis to facilitate the glucose input to hepatocyte</td>
<td>✓</td>
<td></td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td>pck1 [gene]</td>
<td>Increase of expression level</td>
<td>✓</td>
<td></td>
<td>[94, 95]</td>
</tr>
<tr>
<td></td>
<td>PPARα and PPARγ [protein]</td>
<td>Increase of the level and creation of inflammatory effect(s)</td>
<td>✓</td>
<td></td>
<td>[66]</td>
</tr>
<tr>
<td></td>
<td>ACO [protein]</td>
<td>Lowered expression might cause obesity</td>
<td>✓</td>
<td></td>
<td>[96]</td>
</tr>
<tr>
<td></td>
<td>CPT1 [gene]</td>
<td>Increase of expression level possibly leading to obesity</td>
<td>✓</td>
<td></td>
<td>[97]</td>
</tr>
<tr>
<td></td>
<td>PDK4 [gene]</td>
<td>Increase of muscle PDK4 expression</td>
<td>✓</td>
<td></td>
<td>[98]</td>
</tr>
<tr>
<td></td>
<td>TIF2 [gene]</td>
<td>Deletion of this gene protects mice from obese</td>
<td>✓</td>
<td></td>
<td>[75]</td>
</tr>
<tr>
<td></td>
<td>SRC1 [gene]</td>
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<td>✓</td>
<td></td>
<td>[76]</td>
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<tr>
<td></td>
<td>PGC-1α</td>
<td>Activation at neonatal period reduced PDX1 expression and pancreas maturation</td>
<td>✓</td>
<td></td>
<td>[99]</td>
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<tr>
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<td>SIRT1 [gene]</td>
<td>Increase of this gene expression alleviates symptoms in the already diabetic patient</td>
<td>✓</td>
<td></td>
<td>[81]</td>
</tr>
<tr>
<td></td>
<td>slc2a4 [gene]</td>
<td>Reduction of expression that contributes to the impairment of glycemic homeostasis</td>
<td>✓</td>
<td></td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td>Slc2a2 [gene]</td>
<td>Increase of the content and collaboration with nonalcoholic steatohepatitis to facilitate the glucose input to hepatocyte</td>
<td>✓</td>
<td></td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td>pck1 [gene]</td>
<td>Increase of expression level</td>
<td>✓</td>
<td></td>
<td>[94, 95]</td>
</tr>
<tr>
<td></td>
<td>PPARα and PPARγ [protein]</td>
<td>Increase of the level and creation of inflammatory effect(s)</td>
<td>✓</td>
<td></td>
<td>[66]</td>
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<td></td>
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<td></td>
<td>[96]</td>
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<tr>
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<td></td>
<td>SIRT1 [gene]</td>
<td>Increase of this gene expression alleviates symptoms in the already diabetic patient</td>
<td>✓</td>
<td></td>
<td>[81]</td>
</tr>
</tbody>
</table>
While studies on epidemiology related to high-carbohydrate diet related to the risk of T2D development are clearly [18, 102–105], findings about human population study at risk of high-MSG diet are inconsistent. Studies on MSG-related diabetic cases have been frequently reported using animal models. There is a lack of epidemiological data of MSG consumption which contribute to T2D in comparison to those of high-carbohydrate consumption. Epidemiology in Spanish population has been linked to the increasing risks of getting T2D to cardiovascular diseases due to high glutamate plasma level [110]. Based on another epidemiology in Thailand, daily consumption exceeding 5 g of MSG is considered risky to carry metabolic disorders, including T2D [111]. MSG intakes have also been reported to increase the incidence of overweight [112]. However, two studies from the Jiangsu Nutrition Study argued that MSG intake did not correlate with obesity, and even high MSG intake was negatively associated with hyperglycemia [113, 114].

One possible explanation that could explain the opposing results among the studies of epidemiology is the unready transportation from the intestine into the blood circulation in contrast to various experimental data that used MSG-induced diabetic mice models by MSG subcutaneous injection [51, 115]. Another explanation arises from experimental data where life period is an important factor related to the genetic programming by environmental factors. Mice at the age of 4 months old with high-MSG diet are prone to various metabolic disorders, including the increased signs of glucose intolerance. However, along with the aging process, the impairment of metabolism from the obesity effects can be attenuated [116].

By considering both experimental data from animal or cell culture studies with epidemiological data, we summarize that high-carbohydrate diet evidently positively correlates with T2D and could cause the onset of T2D. Although MSG studies are still in conflict with one another, we do not encourage people to slacken their diets by consuming high amount of MSG based on the experimental data of MSG potentials to alter homeostasis on carbohydrate and fat metabolism. All in all, lifestyle intervention shows to be a promising primary prevention of diabetes, and healthy lifestyle is shown to be comparable with metformin intake as reported by Indian Diabetes Prevention Program [104]. Governmental policies can play a huge role on combating the increasing prevalence of diabetes by encouraging a healthy diet and lifestyle, such as taxation program in Thailand for beverages which contain high level of sugar content [117].

Conclusion and future perspectives

High-fat diet is commonly known to induce T2D, especially in the case of high-carbohydrate and high-MSG diets. However, high-MSG diet requires longer time to develop hyperglycemia preceded by obesity. Various genes, especially genes related to glucose and fat metabolism are interrelated within these two diets. Branched signal transduction pathways and different phenotypes of each gene in different organs or ages revealed complicated mechanisms that should be taken as precautions as the targeted gene of interest to treat T2D or to construct a specific biomarker for T2D. Initially, some activated or repressed genes are only a feedback mechanism to control body homeostasis related to the imbalanced diet. For example, high-carbohydrate diet increased SCD-1 expression. Prolonged feedback mechanism often creates vicious cycle thus developing metabolic syndromes including obesity and T2D.

Increasing FoxO1 and ATF4 expressions or their activation in high-carbohydrate-induced diabetic mice will lead to insulin resistance. It could be interesting to study the repression or the side effects of both genes of diabetic mice for long-term experiments. Both genes might have potential uses as a biomarker for early detection of the T2D. The fact of MSG-induced diabetic mice often leads to the increase of gene expressions related to lipogenesis, such as PPARs family. However, the changes in PPARs expression and activation may disrupt the balance between glucose and lipid metabolism. Both TIF2 and SIRT1 are promising genes in alleviating insulin resistance developed from MSG-induced diabetes. However, these strategies have also exhibited some drawbacks. TIF2 silencing increased the expression of PGC-1α that inhibited the maturation of pancreas at neonatal period. Further information on TIF2 silencing of pancreatic cells from various ages of mice models may enlighten the benefits of targeting TIF2 as a gene of interest to treating T2D. It is still unclear how the MSG affects the TIF2 expression in β-cells. Similarly, SIRT1 is indeed an interesting target gene, however, precautions should be taken in drug administration, diet lifestyle, and targeted organs. Otherwise, the disruption of the delicate balance of homeostasis may lead to worsening physical conditions. Studying the SIRT1 signal transduction pathway and its effects on T2D in a more long-term experiment will shed more understanding into how SIRT1 maintains homeostasis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.
Ethical approval The studies conducted in this article do not involve human participants or animals.

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Emantoko_High_Carbohydrate.pdf

by Sulistyo Harsono

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The genetic basis of high-carbohydrate and high-monosodium glutamate diet related to the increase of likelihood of type 2 diabetes mellitus: a review

Joshua Nathanael · Hans Cristian Adhinatya Harsono · Aubrey Druce Wibawa · Putu Guardana · Yoanes Maria Vanney · Sulistylo Emantoko Dwi Putra

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Abstract

Diabetes is one of the most common metabolic diseases. Aside from the genetic factor, previous studies stated that other factors such as environment, lifestyle, and paternal-maternal condition play critical roles in diabetes through DNA methylation in specific areas of the genome. One of diabetic cases is caused by insulin resistance and changing the homeostasis of blood glucose control so glucose concentration stood beyond normal rate (hyperglycemia). High fat diet has been frequently studied and linked to triggering diabetes. However, most Asians consume rice (cooked with high carbohydrate) and food with monosodium glutamate (MSG). This habit could lead to pathophysiology of type 2 diabetes mellitus (T2D). Previous studies showed that high-carbohydrate or high-MSG diet could change gene expression or modify protein activity in body metabolism. This imbalance in metabolism can lead to pleiotropic effects of diabetes mellitus. In this study, the authors have attempted to relate various changes in genes expression or protein activity to the high-carbohydrate and high-MSG-induced diabetes. The authors have also tried to relate several genes that contribute to pathophysiology of T2D and proposed several ideas of genes as markers and target for curing people with T2D. These are done by investigating altered activities of various genes that cause or are caused by diabetes. These genes are selected based on their roles in pathophysiology of T2D.

Keywords High carbohydrate · Insulin resistance · Monosodium glutamate · Obesity · Type 2 diabetes mellitus

Abbreviations

GLUT4 glucose transporter 4
PDX1 pancreatic and duodenal homeobox 1
NKX6.1 NKX6 homeobox 1
MAFA MAFA bZIP transcription factor A
FOXO1 forkhead box protein O1
GRP-78 binding immunoglobulin protein
PERK protein kinase R (PKR)-like endoplasmic reticulum kinase
IRE1α inositol-requiring enzyme 1 α
XRIP X-box binding protein 1
CHOP C/EBP homologous protein
INSIG1 insulin induced gene 1

SREBP-1c sterol regulatory element binding protein 1c
SIRT1 NAD-dependent deacetylase sirtuin-1
SCD1 Stearoyl-CoA desaturase-1
PPAR peroxisome proliferator-activated receptor
ATP4 activating transcription factor 4
CREB-2 cAMP-response element binding protein 2
MEG3 normally expressed 3
SLC2A4 solute carrier family 2 member 4
H3K9me3 trimethylation of lysine 9 on histone H3 protein
PKI phosphoenolpyruvate carboxykinase 1 (soluble)
ACO acetyl-CoA oxidase
CPT1 carnitine palmitoyltransferase 1
BIFEN bifunctional enzyme
ANGPTL4 angiopoietin-like 4

PDK4 pyruvate dehydrogenase lipid kinase isozyme 4
TIF2 transcriptional mediators/intermediary factor 2
UCP3 mitochondrial uncoupling protein 3

Published online: 14 March 2020
Introduction

Diabetic prevalences are continuously increasing and they were predicted to reach 693 million in 2045 [1]. Various factors contributed to the emergence of diabetes ranging from parental genetics [2], maternal epigenetic inheritance due to nutritional imbalances consumption during pregnancy [3], lifestyle, and diet [4, 5]. Physiologically, diabetes could be due to insulin resistance [6], insulin secretory dysfunction [7], or death of pancreas β-cell [8]. The pathogenesis of type 2 diabetes mellitus (T2D) related to obesity has been well reviewed [6]. Epidemic and epigenetics that convey relationship between genetics and environment are closely related to T2D cases [9, 10]. The fact that famine impact on the family health, pregnancy planning, lifestyle, and diet in early stages of pregnancy contributed to future risks of various metabolic disorders, such as obesity and diabetes. This fact has been well-reviewed in the literature [9]. Various environmental factors previously mentioned lead to various epigenetic modifications and cause early insulin resistance associated with the fetal low birth weight [10].

Certain patterns of diets increase the chances of T2D due to alteration in the gene expression. High-fat diet is the most commonly studied and frequently used to induce diabetes [11, 12]. High-fat diets internalize and reduce the expression of pancreatic glucose transporter gene (GLUT2) and glucokinase caused by the hyperglycemia and create a vicious loop of impaired insulin secretion [13, 14]. This diet also reduces the expression of GLUT4 protein and causes insulin resistance in skeletal muscles. High-fat diets also inactivated insulin receptor substrate (IRS-1) in liver and caused inflammation in mice models [15]. Methylation studies on PDK4 also revealed that high-fat-diet-induced methylation on a specific CpG site before the onset of hyperglycemia as one proof of epigenetic regulation plays an important role in metabolic disorder [16].

Primary food with high glycemic index, such as rice, is a staple food for more than half of the world’s population in various Asian countries [17]. High carbohydrate diet, such as refined grain is also associated with an increased risk of T2D [18–20]. High sucrose and fructose diets are also contributing factors to T2D since sucrose and fructose cause pancreas and liver toxicity [21–23]. Another relevant Asian food additive that can induce T2D is the high intake of MSG [24–28]. Epigenetically, a newborn female in the suckling period who eats a high-carbohydrate diet has been reported to readily develop hyperinsulinemia and to acquire obesity in the adulthood [29]. The second generation of these female rats spontaneously develop the similar phenotype even without any intervention studies indicating maternal fetal programming [29]. MSG-induced obesity by subcutaneous injection of female Wistar rats’ parent, has been reported to bring forth male offspring that experienced various metabolic disorders, such as insulin and leptin resistance [30]. These initial facts implied that both high-carbohydrate and high-MSG diets contribute to the emergence of T2D.

To the extent of the authors’ literature reviews, diets with high carbohydrate and high MSG have not been so extensively reviewed as those with high fat (especially in the consequences of high-carbohydrate and high-MSG intakes on gene expression). This review focuses on exploring the genetic interactions of both diet patterns that leads to T2D. Literature reviews related to T2D and human central metabolism were employed to initially screen some genes or proteins that have been extensively studied. Then, the possibilities of alteration of these genetic expressions using carbohydrate and MSG adjustment were also investigated. Thus, this review can provide insights into the screening processes of genes that can serve as potential biomarkers in T2D prediction. The genes or the proteins can also offer possible breakthroughs in therapies for T2D patients.

Genetic aspects that promote T2D: high-carbohydrate diet study

High-carbohydrate feeding after a period of time of non-carbohydrate diets caused the mice to enter fast hyperglycemic period [13]. The high-carbohydrate diet in mice models dephosphorylate FoxO1 without reducing its expression where the phosphorylation was regulated in Akt pathway. As FoxO1 stayed in the nucleus and significantly reduced the expression of PDX1, NKF1, and MAFA genes that are essential for the survival and the maintenance of β-pancreas cell and insulin production [13, 31, 32]. High-fructose diets were also found to increase both the m-RNA content of FoxO1 and the expression of pancreatic GRP-78, PERK, IRE1α, XBP1, CHOP gene, hepatic GRP-78, and caspase activity [21]. All these genes belong to the family of endoplasmic reticulum stress markers and relate to cell death. Interestingly, high fructose diets also reduce the expression of INSIG1 [21]. This is the protein that regulates SREBP-1c that is important to synthesize fat when the cells are rich in carbohydrate [33]. In contrast, activation and retention of FoxO1 in the nucleus by deacetylation are essential to protect β-pancreas
Endocrine
cell of diabetic mice within the long term by reducing the
dependence on fatty acid oxidation as energy source [34].
This signifies that FoxO1 activation might be one approach
of our body to control homeostasis.
Animal models showed that high-carbohydrate diet
upregulated the expression of hepatic acetyl-CoA carboxylase
stearyl-CoA desaturase 1 gene (Scdl), while Scdl normally
is not expressed in liver but expressed constitutively
in adipose tissue [35–38]. High-carbohydrate diet was found
to increase the expression of various elongase and
desaturase enzymes that synthesize unsaturated fatty acid,
especially monounsaturated fatty acid in liver [39]. Scdl
activation initiated vicious cycle which created insulin
resistance. Downregulation of Scdl proved to increase the
phosphorylation of AKT and to alleviate the insulin resis-
tance [40–43].
 Although Scdl might be an interesting gene to be
downregulated, Scdl deficiency alone was found to be
insufficient to protect mice from getting obese [44]. In
contrast, the activation of Scdl gene specifically in skeletal
muscle enhanced the activation of PPAR-β to oxidize fat
and increased the metabolism in skeletal muscles that could
protect T2D mice from obesity [45]. This opposing
phenotype in skeletal muscles and hepatic cells both arising
from the activation of Scdl expression denoted that each
protein behaves differently and possibly targets different
proteins in each organ. The Scdl gene correlation with
high-carbohydrate diet has been investigated for more than
two decades but with no firm consequences. Care must be
taken when making a research to silence this gene or to
make an inhibitor for Scdl. Clearly, more data are needed
to be able to map the effect of Scdl on not only various genes
but also various organs.
ATF4 (or CREB2) deficiency has been shown to suppress
the expression of SCD1 in liver, and ATF4-deficiency mice
has lower fat content compared with the normal genotype.
In high-carbohydrate diet mice, deletion of ATF4 improved
insulin sensitivity and caused hypoglycemia [46, 47]. ATF4
deletion also significantly reduced the expression of hepatic
PPARγ which contributed to lipid genesis resulting in
reduction of other genes expression involved in lipogenesis
such as SREBP-1c and acetyl-CoA carboxylase. ATF4
deletion also protected high-fructose diet mice from
developing hyperglycemia and liver steatosis [48]. This
fact was further enhanced by the downregulation of ATF4 in
liver by miRNA-214 that could alleviate glucosegenosis
and reduce the expression of FoxO1 in high-fat diet mice
[49]. MEG3, a noncoding RNA, was found to be a com-
peting endogenous RNA for miRNA-214 that resulted in
increase of ATF4 and FoxO1 expression which create insulin
resistance [50]. These facts might seem that downregulating
ATF4 or regulating the miRNA-214-MEG3 axis can be a
promising way to combat T2D. Nevertheless, referring to
the contrasting long-term effect of FoxO1 [34], more data
are required to observe long-term effects of ATF4 up- or
downregulation on the diabetic animal models.

Evenly, nutritional factors of high-carbohydrate and
high-fat diet-induced diabetic mice overlap with each other
in the genetic pathways when a different metabolic pathway
is used. This condition possibly occurs when food enters the
body and several mechanisms of metabolisms interact with
each other to form a complex mechanism to maintain
homeostasis. Prolonged imbalanced diet or excessive car-
bohydrate consumption may lead to pathophysiology of
T2D. The idea of some gene expression and protein activity
alterations when the body encounters high-carbohydrate diet
is summarized in the following Figs. 1 and 2.

Genetic aspects that promote T2D: high-
MSG intervention study

Monosodium glutamate (MSG) has been linked with var-
ious metabolic disorders. Metabolism of MSG by dietary
intake is well reviewed [51]. Glutamate is a nonessential
amino acid that is usually oxidized or acted as precursor for
other amino acids in gut. With excess of MSG intakes, the
intestine capacity to absorb MSG remain unchanged. In
neonatal primate, high dose of MSG administered by gastric
tube, induced elevation of glutamate, and aspartate content
(the result of glutamate metabolism by liver) after 1 week of
treatment without any lesion in neuron [52]. Thus, MSG
is considered as GRAS food additive.

Here, the focus of the study is the genetical and experi-
mental effects of MSG intervention study toward expression
of genes and metabolism. However, it should be taken into
account that various experimental data used MSG injection
to develop obesity and hyperglycemic animal models to
reveal the genetic architecture between MSG and T2D.
MSG is also now a suspected obesogen—a small chemical
that could disrupt fat metabolism and appetite [53]. MSG
was found to impair pro-hormone-like peptide (GLP-1) secre-
tion in cell model, a peptide hormone that is important for
βcell growth, and insulin production [54]. In short term
(3 h), secretion of GLP-1 was increased, but in chronic term
(72 h), cytotoxicity was observed and there was a reduction
in GLP-1 secretion [55].

MSG-induced hyperglycemia caused the same insulin
resistance phenomenon induced by streptozotocin. MSG
also caused obesity in the nongenetic mice models. How-
ever, MSG-induced diabetic mice did not experience an
increase in expression of TNF-α, a marker that is usually
used to indicate obesity and might also cause diabetes
[56, 57]. No reduction of pancreatic β-cell in the MSG-
induced diabetes was observed compared with that in the
streptozotocin-induced diabetes [25].
Fig. 1 Mechanism of high-carbohydrate and high-fructose diets affecting gene expression and protein activity

Fig. 2 Changes of gene expression by MSG-induced diabetes in neonatal period

MSG-induced diabetic mice exerted decreased content of GLUT4 protein (not GLUT1), disrupt glucose utilization, and caused insulin resistance [58]. This is due to methylation of Sreca1 promoter area that produced GLUT4 by H3K9me3 using gastroenteritis skeletal cell [59]. An increase of Sreca1 gene expression (encoding GLUT2) and pck1 (encoding key enzyme in gluconeogenesis in the liver) was also induced in MSG-diabetic mice. This increase caused glucose outflow and created hyperglycemia [60].

MSG-induced diabetes also takes a longer time to develop hyperglycemia phenomenon, and the obesity period is usually the first indicator [26, 61, 62]. Subcutaneous injection of rats with MSG reduced the expression of genes related to fat oxidation, such as PPARα, ACO, CPT1, and BIFEEZ [64, 65]. Conversely, MSG-induced diabetic mice in neonatal period gain an increase of expression in PPARα and PPARγ and inflammation [66]. Although both mechanisms are intertwined, MSG observably induced the lipogenesis Chiglitazar, the agonist PPARα and PPARγ, is reported to inhibit the phosphorylation of PPARγ, thus deactivates the protein and increases the expression of ANGPTL4 and PDK4 [67-69]. ANGPTL4 is a protein that protects human from getting obese and myocardial infarction due to high-fat diet by inhibiting the lipoprotein lipase activity, reducing free fatty acid levels in serum [70]. PDK4 is an enzyme that turns off the pyruvate dehydrogenase and in turn, activates the β-oxidation pathway that is often expressed in skeletal muscle cell, and can be repressed by insulin. An increase of PDK4 expression is often observed in diabetic patients and increases insulin resistance and dependence on fatty acids oxidation as energy source [71, 72]. However, in a short-term high-fat diet, the increase of PDK4 expression is important to balance the glucose and fat level. The increase of ANGPTL4 and PDK4 expression is regarded as the feedback mechanism to protect cells from fatty acid-induced oxidative stress [73, 74].

The loss-of-function experiment using skeletal muscle cells and adipocytes on TIF2 revealed PPARγ expression reduction [75]. The deletion of TIF2 reduced the expression of lipoprotein lipase, aP2, and increased lipolysis and the resistance of MSG-diabetic induced mice from getting obese in combination with SRC1 expression for better energy expenditure [75]. Experiment on TIF2−/− mouse supported the idea about the role of TIF2 on obesity whereas TIF2 and SRC1 act antagonistically toward UCP3 expression [76]. Silencing TIF2 gene increased the expression of UCP3 and in turn, increased body
metabolism, and reduce weight gain [77]. Loss-of-function of TIF2 also induced the expression of PGC-1α in skeletal muscle cells, and the expression increased the oxidative metabolism of muscle cell [76, 78]. SRC3 deletion on mice also increased the PGC-1α activity by reducing acetylation on skeletal muscle cells [79]. However, expressed PGC-1α raised different phenotypes from different organs and periods of induction. Pancreatic overexpression of PGC-1α in neonatal period inhibited the expression of PDX1. The inhibition of PDX1 expression caused dysfunction and mass reduction in pancreatic β-cell. However, PGC-1α overexpression in the adult mice did not affect the pancreatic β-cell [80].

Recently, SIRT1, a histone deacetylase protein, has been proved to increase insulin sensitivity. SIRT1 expression improved glycemic control and insulin sensitivity on liver, muscle, adipose tissue, and β-cell pancreas [81, 82]. It is further supported by mice that are deficient in SIRT1 which develop hyperglycemia and insulin resistance [83]. MSG-induced diabetic mice does not seem to cause any changes in SIRT1 expression level. However, various ligands that act as SIRT1 activator such as resveratrol, SRT1720, and MHI2233, improved the steatosis condition [60, 84, 85]. In contrast, genetic diabetic db/db mice reportedly were in use [86]. Although the activation of SIRT1 did stimulate the pancreatic β-cell plasma insulin concentration, SIRT1 activation caused a reduction in body temperature and metabolism (torpor condition) with more long-term effects of weight gain and hepatic steatosis [85].

However, acute knockout of SIRT1 lead to reduction of hyperglycemia setting and an increase of insulin sensitivity by increasing the liver responsiveness to insulin and reducing gluconeogenesis [87, 88]. The results regarding SIRT1 effects on gluconeogenesis and insulin sensitivity seem inconsistent. This discrepancy could be due to the feedback mechanism on the SIRT1-FOXO1 pathway by SHP (encoded by Nrotb) [89]. Furthermore, SIRT1 knockout in healthy mice brings normal fed and fasting blood glucose level [89]. However, SIRT1 knockout in genetic diabetic mice (double knockout on IRS1/2) resulted in better blood glucose level and glucose tolerance, although the mice were still insulin resistant. This implied that SIRT1 activation can be completed in genetically derived diabetic patients or in already diabetic patients. SIRT1 treatment might not be used to prevent people from diabetes.

In general, MSG-induced mice are more related to obese phenotype. Quite a few involved genes are intertwined with obesity, such as fat metabolism from PPARs family. While high-carbohydrate-induced diabetes can also cause lipogenesis by balancing the excess of carbohydrate into fat, MSG-induced diabetes seems to directly activate lipogenesis. The changes in genes expression triggered by MSG-induced T2D are summarized in Fig. 3.

**Involvement of genes and proteins in T2D**

It is important to figure out whether the disruption of the gene expression is the reason for the T2D, or whether the disruption is generated by the T2D. There are two categories were used to sort some genes whether the genes induce T2D, or T2D changes the genes expression (Table 1). The genes that could affect T2D development might be used as diabetes markers and targeted to prevent T2D. While some gene expressions that are altered after T2D has occurred can be treated to alleviate the diabetes symptoms. The delicate interaction of the proteins, such as pleiotropic effects and highly branched signaling pathways and feedback mechanisms, also complicates the treatment of the targeted gene without disrupting the homeostasis of our body. Genes or proteins whose activities are altered after diabetes and increase diabetes severity, or the further missing link that still has to be developed is placed in not determined (ND).

Various genes such as FOXO1, PDX1, ATF4, and INSIG1 proved to be important for the development of β pancreas cells, or to maintain the balance of metabolism to increase glucose tolerance. Meanwhile, genes expression alteration that directly correlate with carbohydrate or fat metabolism, such as GLUT 6, pck1, scd1, and PPARG are more likely caused by feedback mechanism and complex regulation to give better glucose level performa [60, 97]. Disturbance of expression in genes like ACO, CPT1, TIF2, SRC1, scd1, and UCP3 in muscle cells and adipocyte cells are more into causing obesity, in which these genes are related to fat metabolism and energy expenditure. Caution must be taken that diabetes could also ablated these genes expression directly related to metabolism and disruption of these genes in early stage of development could also cause various physiological imbalances. However, genes like TIF2, SRC1, and PGC-1α were predicted to be more upstream in the signaling pathway. Thus, modulation of these genes might prevent further physiological aberrations related to metabolism imbalances such as obesity and diabetes. SIRT1 expression was not changed by diabetes and its knockout also did not cause T2D. SIRT1 is a promising gene to be targeted in the already diabetic patient as previously stated above. We further hypothesized that based on the animal studies, both high carbohydrate (found in high glycemic index food or energy-dense food) and introduction of high MSG (by injection) might reinforce each other to increase the prevalence of T2D or other metabolic disorders. The possibility of intervention study employing both factors might be noteworthy to be investigated.
Population-based studies of high-carbohydrate and high-MSG diet

Using animal and cell line models, high-MSG and high-carbohydrate diets correlated and might also contribute to the onset of T2D by disrupting expression and the activity of various genes mentioned in Table 1. However, studies on epidemiology might support or contrast the idea of the correlation between T2D and high-MSG or high-carbohydrate diet. Various factors contributed to this conditions such as age, ethnicity, genetics, anatomical and metabolic differences, or socioeconomics or even in the experimental design itself [100].

Population study of dietary carbohydrate intake above normal level in Japanese population showed that obese participants develop T2D more readily than nonobese participants. This indicated that large samples, genetic effects, participants’ backgrounds should be considered in the epidemiology study [101]. However, epidemiological studies in China, India, United States, and UAE supported the dietary style of high-carbohydrate intake (such as refined grain and added sugar) positively correlated with T2D [18, 102-105]. Another profound study on epidemiology related to the increasing risk of T2D was conducted on sugar-sweetened diet beverages in female US nurses in 1989 [106]. The intake of these high-calorie beverages (such as, soft drink and fruit punch) was said to be associated with the increasing chances of T2D development. More than 60% diabetic people live in China and India, followed by Japan [103, 107]. Asian countries, such as China, India, or UAE are predicted to yield a higher rate of diabetic prevalence [18, 102-105]. Although general
Table 1 Summary of genes involved in diet-induced diabetes

<table>
<thead>
<tr>
<th>Diet</th>
<th>Gene/protein</th>
<th>Effect</th>
<th>Condition Changed by T2D</th>
<th>Affecting T2D development</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>High carbohydrate</td>
<td>FoxO1 [protein]</td>
<td>Dephosphorylated</td>
<td>✓</td>
<td>✓</td>
<td>[13]</td>
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<tr>
<td></td>
<td>S6K1 [gene]</td>
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<td>✓</td>
<td>[36]</td>
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<td>✓</td>
<td>[48]</td>
</tr>
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<td></td>
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<td>Reduction of expression</td>
<td>✓</td>
<td>✓</td>
<td>[90]</td>
</tr>
<tr>
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<td>FoxO1 [gene]</td>
<td>Increase of expression</td>
<td>✓</td>
<td>✓</td>
<td>[90]</td>
</tr>
<tr>
<td>High-MSG</td>
<td>GLUT4 [protein]</td>
<td>Reduction of expression accompanied with whole-body insulin resistance and increased plasma secretion of inflammatory markers</td>
<td>✓</td>
<td>✓</td>
<td>[91]</td>
</tr>
<tr>
<td></td>
<td>S6K2a1 [gene]</td>
<td>Reduction of expression that contributes to the impairment of glycemic homeostasis</td>
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<td>✓</td>
<td>[92]</td>
</tr>
<tr>
<td></td>
<td>S6K2a2 [gene]</td>
<td>Increase of the content and collaboration with nonalcoholic steatohepatitis to facilitate the glucose input to hepatocyte</td>
<td>✓</td>
<td>✓</td>
<td>[93]</td>
</tr>
<tr>
<td></td>
<td>pp11 [gene]</td>
<td>Increase of expression level possibly leading to obesity</td>
<td>✓</td>
<td>✓</td>
<td>[94, 95]</td>
</tr>
<tr>
<td></td>
<td>PPARα and</td>
<td>Increase of the level and creation of inflammatory effect(s)</td>
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<td>✓</td>
<td>[66]</td>
</tr>
<tr>
<td></td>
<td>PPARγ [protein]</td>
<td>Lowered expression might cause obesity</td>
<td>✓</td>
<td>✓</td>
<td>[96]</td>
</tr>
<tr>
<td></td>
<td>ACO [protein]</td>
<td>Increase of expression level possibly leading to obesity</td>
<td>✓</td>
<td>✓</td>
<td>[96]</td>
</tr>
<tr>
<td></td>
<td>CPT1 [gene]</td>
<td>Increase of expression level possibly leading to obesity</td>
<td>✓</td>
<td>✓</td>
<td>[97]</td>
</tr>
<tr>
<td></td>
<td>PDK4 [gene]</td>
<td>Increase of muscle PDK4 expression</td>
<td>✓</td>
<td>✓</td>
<td>[98]</td>
</tr>
<tr>
<td></td>
<td>TIF2 [gene]</td>
<td>Deletion of this gene protects mice from obesity</td>
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<td>✓</td>
<td>[75]</td>
</tr>
<tr>
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<td>SRC1 [gene]</td>
<td>Antagonist of TIF2</td>
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<td>✓</td>
<td>[76]</td>
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<tr>
<td></td>
<td>PGC-1α [gene]</td>
<td>Activation at neonatal period reduced PDX1 expression and pancreas maturation</td>
<td>✓</td>
<td>✓</td>
<td>[99]</td>
</tr>
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<td>Increase of this gene expression alleviates symptoms in the already diabetic patient</td>
<td>✓</td>
<td>✓</td>
<td>[81]</td>
</tr>
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<td></td>
<td>S6K2a1 [gene]</td>
<td>Reduction of expression that contributes to the impairment of glycemic homeostasis</td>
<td>✓</td>
<td>✓</td>
<td>[92]</td>
</tr>
<tr>
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<td>S6K2a2 [gene]</td>
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<td>✓</td>
<td>[93]</td>
</tr>
<tr>
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<td>pp11 [gene]</td>
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<td>✓</td>
<td>[94, 95]</td>
</tr>
<tr>
<td></td>
<td>PPARα and</td>
<td>Increase of the level and creation of inflammatory effect(s)</td>
<td>✓</td>
<td>✓</td>
<td>[66]</td>
</tr>
<tr>
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<tr>
<td></td>
<td>SRC1 [gene]</td>
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<td>[76]</td>
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<tr>
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<td>Increase of this gene expression alleviates symptoms in the already diabetic patient</td>
<td>✓</td>
<td>✓</td>
<td>[81]</td>
</tr>
</tbody>
</table>

population in Japan consume white rice and MSG-enriched food like people in other Asian countries, uniquely, Japan is projected to have only a small increase in the ratio of its diabetic people in 2025. This fact might be due to the nationwide health guidance and lifestyle intervention program [107–109].
While studies on epidemiology related to high-carbohydrate diet related to the risk of T2D development are clearly [18, 102–105], findings about human population study at risk of high-MSG diet are inconsistent. Studies on MSG-related diabetic cases have been frequently reported using animal models. There is a lack of epidemiological data of MSG consumption which contribute to T2D in comparison to those of high-carbohydrate consumption. Epidemiology in Spanish population has been linked to the increasing risks of getting T2D to cardiovascular diseases due to high glutamate plasma level [110]. Based on another epidemiology in Thailand, daily consumption exceeding 5 g of MSG is considered risky to carry metabolic disorders, including T2D [111]. MSG intakes have also been reported to increase the incidence of overweight [112]. However, two studies from the Jiangsu Nutrition Study argued that MSG intake did not correlate with obesity, and even high MSG intake was negatively associated with hyperglycemia [113, 114].

One possible explanation that could explain the opposing results among the studies of epidemiology is the unzipped transportation from the intestine into the blood circulation in contrast to various experimental data that used MSG-induced diabetic mice models by MSG subcutaneous injection [51, 115]. Another explanation arises from experimental data where life period is an important factor related to the genetic programming by environmental factors. Mice at the age of 4 months old with high-MSG diet are prone to various metabolic disorders, including the increased signs of glucose intolerance. However, along with the aging process, the impairment of metabolism from the obesity effects can be attenuated [116].

By considering both experimental data from animal or cell culture studies with epidemiological data, we summarize that high-carbohydrate diet evidently positively correlates with T2D and could cause the onset of T2D. Although MSG studies are still in conflict with one another, we do not encourage people to slacken their diets by consuming high amount of MSG based on the experimental data of MSG potentials to alter homeostasis on carbohydrate and fat metabolism. All in all, lifestyle intervention shows to be a promising primary prevention of diabetes, and healthy lifestyle is shown to be comparable with metformin intake as reported by Indian Diabetes Prevention Program [104]. Governmental policies can play a huge role on combating the increasing prevalence of diabetes by encouraging a healthy diet and lifestyle, such as taxation program in Thailand for beverages which contain high level of sugar content [117].

Conclusion and future perspectives

High-fat diet is commonly known to induce T2D, especially in the case of high-carbohydrate and high-MSG diets. However, high-MSG diet requires longer time to develop hyperglycemia preceded by obesity. Various genes, especially genes related to glucose and fat metabolism are interrelated within these two diets. Branched signal transduction pathways and different phenotypes of each gene in different organs or ages revealed complicated mechanisms that should be taken as precautions as the targeted gene of interest to treat T2D or to construct a specific biomarker for T2D. Initially, some activated or repressed genes are only a feedback mechanism to control body homeostasis related to the imbalanced diet. For example, high-carbohydrate diet increased SCD-1 expression. Prolonged feedback mechanism often creates vicious cycle thus developing metabolic syndromes including obesity and T2D.

Increasing FoxO1 and ATF4 expressions or their activation in high-carbohydrate-induced diabetic mice will lead to insulin resistance. It could be interesting to study the repression or the side effects of both genes of diabetic mice for long-term experiments. Both genes might have potential uses as a biomarker for early detection of the T2D. The fact of MSG-induced diabetic mice often leads to the increase of gene expressions related to lipogenesis, such as PPARs family. However, the changes in PPARs expression and activation may disrupt the balance between glucose and lipid metabolism. Both TIF2 and SIRT1 are promising genes in alleviating insulin resistance developed from MSG-induced diabetes. However, these strategies have also exhibited some drawbacks. TIF2 silencing increased the expression of PGC-1α that inhibited the maturative process of pancreas at neonatal period. Further information on TIF2 silencing of pancreatic cells from various ages of mice models may enlighten the benefits of targeting TIF2 as a gene of interest to treating T2D. It is still unclear how the MSG affects the TIF2 expression in β-cells. Similarly, SIRT1 is indeed an interesting target gene, however, precautions should be taken in drug administration, diet lifestyle, and targeted organs. Otherwise, the disruption of the delicate balance of homeostasis may lead to worsening physical conditions. Studying the SIRT1 signal transduction pathway and its effects on T2D in a more long-term experiment will shed more understanding into how SIRT1 maintains homeostasis.

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Conflict of interest The authors declare that they have no conflict of interest.
Endocrine

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