Life-style-induced metabolic derangement and epigenetic changes promote diabetes and oxidative stress leading to NASH and atherosclerosis severity

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Received: 30 April 2018 / Accepted: 20 November 2018 / Published online: 29 November 2018
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Abstract

Energy imbalance resulting from high calorie food intake and insufficient metabolic activity leads to increased body mass index (BMI) and sets the stage for metabolic derangement influencing lipid and carbohydrate metabolism and ultimately leading to insulin resistance, dyslipidemia, and type 2 diabetes. 70% of cardiovascular disease (CVD) deaths occur in patients with diabetes. Environment-induced physiological perturbations trigger epigenetic changes through chromatin modification and leads to type 2 diabetes and progression of nonalcoholic fatty liver disease (NAFLD) and CVD. Thus, in terms of disease progression and pathogenesis, energy homeostasis, metabolic dysregulation, diabetes, fatty liver, and CVD are interlinked. Since advanced glycation end products (AGEs) and low-grade inflammation in type 2 diabetes play definitive roles in the pathogenesis of liver and vascular diseases, a natural checkpoint to prevent diabetes and associated complications appears to be the identification and management of prediabetes together with weight management, since 70% of prediabetic individuals develop diabetes during their life time, and every kg of weight increase is associated with up to 9% increase in diabetes risk. A good proportion of diabetes and obesity population have fatty liver that progresses to non-alcoholic steatohepatitis (NASH) and cirrhosis, and increased risk of hepatocellular carcinoma. Diabetes and NASH both have elevated oxidative stress, impaired cholesterol elimination, and increased inflammation that leads to CVD risk. This review addresses life-style-induced metabolic pathway derangement and how it contributes to epigenetic changes, type 2 diabetes and NASH progression, which collectively lead to increased risk of CVD.

Keywords Life-style · Diabetes · Epigenetic · Cardiovascular · NASH · Inflammation · Atherosclerosis

Abbreviations

VLDL	very low-density lipoprotein
LDL	low-density lipoprotein
HDL	high-density lipoprotein
CVD	cardiovascular disease
NAFLD	non-alcoholic fatty liver disease
AGE	advanced glycation end-products
NASH	non-alcoholic steatohepatitis
MetS	metabolic syndrome
apoA-I	apolipoprotein A-I
BMI	body mass index
miR	micro RNA

COPD	chronic obstructive pulmonary disease
HAT	histone deacetylase
HDAC	histone acetyl transferase
T2DM	type 2 diabetes mellitus
VSMC	Vascular smooth muscle cells
MCP1	monocyte chemoattractant protein 1
LSD-1	lysine-specific demethylase
VCAM1	vascular cell adhesion molecule 1
NF-κB	nuclear factor kappa B
Cox2	cyclooxygenase 2
TNF-α	tumor necrosis factor-α
FXR	farnesoid X receptor
TRL	triglyceride-rich lipoproteins
RCT	reverse cholesterol transport
SR-BI	scavenger receptor class B type 1
ABCA1	ATP binding cassette transporter 1
HbA1c	hemoglobin A1c
RAGE	receptor for advanced glycation end-products

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Introduction

The dramatic increase in the prevalence of diabetes in the past two decades has led to an alarming increase in the cardiovascular disease (CVD) risk. Currently, 68% of diabetic people die of CVD-related mortality and 16% die of stroke. (AHA Report) [1]. Life style has significantly contributed to the risk factor commonly referred to as Metabolic Syndrome (MetS) [2–5], characterized by dyslipidemic profile [6, 7] with proatherogenic triglyceride-rich VLDL [8–11] leading to oxidative stress and inflammation [12, 13], high triglycerides [14], and low levels of HDL [15] together with insulin resistance [16] and impaired glucose tolerance [17] and, in majority of cases, hypertension [18]. Collectively, these abnormalities serve as a precursor to initiate the pathogenesis of diabetes and ultimately leading to cardiovascular disease (Fig. 1). What has caused this disproportional increase in diabetic population to the extent of becoming epidemic? Shall we blame our genetic make-up or the environment, or a combination of both? Published literature and huge collection of scientific evidence suggest that in the past 3 decades life-style, especially energy imbalance due to high calorie food intake, has led to marked derangements in the metabolic pathways of lipid and carbohydrates and contributed to setting the stage for the progression of metabolic disease [19, 20]. The environment, life-style, and energy imbalance combination has largely contributed to the onset of diabetes and significantly elevated the risk of heart disease, the number one killer in the Western society and rapidly becoming one of the major causes

of mortality and morbidity in the developing countries through increased incidence of diabetes.

Obesity causes insulin resistance and diabetes

Weight gain as a result of high calorie food intake and life-style changes appears to be associated with the development of prediabetes and insulin resistance [21] that sets the stage for developing diabetes (Fig. 1). The dramatic increase in the level of mean BMI in the United States [22, 23] and in many other developed and developing countries is an indication of how life-style has contributed to the development of obesity leading to insulin resistance and prediabetic stage [24]. For every kg of weight gain diabetes risk increases by 4.5–9% [25]. With increases in adiposity the risk of developing diabetes, hypertension, and cardiovascular disease also increases. Obesity triggers systemic metabolic dysregulation causing chronic lipid oversupply and leading to tissue dysfunction and disease development. These lipid-induced functional impairments occur in the major peripheral organs like adipose tissue, liver, skeletal muscle, and pancreas [26]. Thus, principal contributor to the obesity-induced progression of insulin resistance and metabolic dysfunction is the alterations in plasma lipid and lipoprotein levels. The dyslipidemic profile in obesity is commonly manifested as high plasma triglyceride levels, low high-density lipoprotein cholesterol (HDL), and production of small dense LDL particles [27]. Other factors

Fig. 1 Energy imbalance leads to obesity. High calorie intake and sedentary life-style leads to net gain as fat mass and hyperlipidemia resulting in the induction of insulin resistance, which progresses to diabetes and impaired insulin secretion by pancreatic beta cells. In the process of insulin resistance elevated and inflamed adipose cells play an

important role through secretion of cytokines, known to be contributing factors in impairing insulin signaling pathway and suppressing pancreatic insulin production/secretion. This results into the impaired uptake of glucose by the muscles and ultimately causing hyperglycemia

have also been suggested to contribute to the obesity-induced alterations in metabolism. One of them is the low apoA-I and low HDL resulting from higher HDL-apoA-I fractional catabolic rate and lower HDL-apoA-I production rate [28].

Fructose-containing diets are shown to cause insulin resistance and increased BMI in preclinical models [29, 30]. It is therefore very likely that the fructose-containing beverages as well as high calorie “comfort” food have impacted mean BMI and visceral fat in individuals in the developed and developing countries like India and China, where incidence of diabetes is growing at an alarming rate [31]. According to WHO 2016 report, in India alone, almost 9% population is diabetic (World health) [32]. The incidence in big cities are even higher in the range of 15–20% [33]. This does not include those who have not been diagnosed or those who are prediabetic. In China, as per WHO report, 10% of adults, excluding those with prediabetic profile, have diabetes [34]. If we take into consideration the prediabetic population, the numbers are even more scary [35]. These data are important in terms of not only the seriousness of the problem, but also the factors that lead to setting the stage and contributing to the progression of diabetes. One factor that contributed most to diabetes progression is certainly the life-style across populations in the low- and middle-income countries than in high-income countries, resulting in a rapid rise in diabetes population, which was associated with higher percentage of death attributable to diabetes and higher blood glucose prior to age 70. United Nations 2017 population report suggest that as of 2014, the combined population of India (1.27 billion) and China (1.37 billion) is estimated to be about 2.64 billion. One can easily project the amount of diabetic population adding each year in addition to growing numbers of individuals with prediabetes.

Life-style-induced epigenetic changes induce diabetes

What we eat (environment) and how we live (life-style) appears to have marked influence on how our genes behave. Lifestyle diseases are a result of the inappropriate relationship of humans with their environment. Imbalance in the normal body metabolism as a result of life-style and environment has been shown to have its imprints on genetic material in the form of modified DNA without alteration in the DNA sequence and this modification gets transmitted to new cells after mitotic division and to generation. This process of inheritable modifications in DNA is termed as *epigenetics* [36].

Epigenetics include both DNA and histone protein modifications as well as micro RNAs. When gene splicing mechanism and the exon-intron sequences was first described 4 decades ago by Chambon [37], it was thought that unlike prokaryotes, majority of DNA present as introns and noncoding sequences have no function in humans [38]. For the past

15 years, researchers have discovered that these intronic and noncoding DNA sequences have important biologic functions since they code for microRNA (miR) of 20–25 nucleotides and long non-coding RNAs (>200 nt) that regulate 3-dimensional structure of chromatin and facilitate DNA modifications leading to up- or down-regulation of genes that contribute to or attenuate disease progression (Fig. 2).

Epigenetics include DNA and histone protein modifications as well as micro RNAs. Recent scientific evidence suggests that these epigenetic mechanisms give rise to lifestyle disease [39, 40]. DNA methylation is the most abundant epigenetic modification that directly affects the function of a gene in eukaryotes [41, 42]. Apart from histone methylation/ demethylation [43], acetylation and deacetylation are other modifications in histone proteins carried out by two enzymes, histone deacetylase (HDACs) and histone acetyl transferase (HAT) [44–46].

Liver, muscle, adipose, and pancreas are major tissues experiencing metabolic dysfunction in diabetic conditions [19]. DNA modifications in the genes associated with diabetes in these tissues may trigger the progression of diabetes. Histone modifying enzymes contribute to the activation or inactivation of transcription by catalyzing the unfolding or further compaction, respectively, of chromatin structure. As depicted in Fig. 2, life-style, environment as well as genetic factors influence chromatin structure and contribute to diabetes progression [47]. Diabetes independently influence DNA modification leading to epigenetic changes that transmits to next generation [48]. These epigenetic changes could be both

Fig. 2 Life-style induces epigenetic modification of DNA through chromatin remodeling, which remains in the cell as metabolic memory. Epigenetic changes can lead to diabetes and diabetes can lead to epigenetic changes. Thus, life style and environment influences diabetes progression both directly as well as indirectly via DNA modification and epigenetic changes. On the other hand, hyperglycemia induces DNA modification through modulation of histone modifying enzymes

a gain of function or a loss of function and through metabolic memory gets transmitted to the dividing cells and contributes in the progression of diabetes and CVD [40]. To look into a link between diabetes and epigenetic modification, a thorough analysis was made by Wren and Garner [49] using parameters like genes, diseases, phenotypes, and chemical compounds from electronically available scientific literature relating to T2DM. This comprehensive analysis was undertaken to find out what novel factors implicate in the pathology of T2DM. Among several parameters analyzed, epigenetic factors turned out to be among the highest statistically significant, implying epigenetic changes within the body as causal factors in the pathogenesis of T2DM.

In pancreatic beta cells hyperacetylation of histones of some of the genes is suggested to be required for glucose homeostasis [50]. In addition, insulin gene which is exclusively expressed in the pancreatic beta cells is regulated by the chromatin structure and polymerase 2 recruitment at the insulin gene promoter [51]. This regulation was dependent on the dimethylated histone H3-Lys-4 at the insulin promoter. Further analysis revealed that Set9 is expressed in an islet-enriched pattern in the pancreas, similar to the pattern of transcriptional activator, Pdx-1, expression [52, 53]. Other studies have also showed that hyperglycemia leads to epigenetic changes. When mouse insulinoma 6 cells were exposed to high glucose concentration, it resulted in hyperacetylation of histone 4 at the insulin gene promoter that correlated with the level of insulin gene transcription [54]. Indeed, actively transcribed genes are typically hyperacetylated at Lys residues of histones H3 and H4 and hypermethylated at Lys-4 of histone H3 (H3-K4). Chakraborty et al. [55] found that insulin promoter is hyperacetylated at histone H3 only in beta cells and highly correlated to recruitment of the histone acetyltransferase p300 to the proximal promoter in beta cells, and is consistent with the role of hyperacetylation in promoting euchromatin formation. The proximal insulin promoter of beta cells was found to be hypermethylated at H3-K4, and that this modification was correlated to the recruitment of the histone methyltransferase SET7/9 to the promoter (Fig. 3).

It has been shown that despite achieving glycemic control, diabetic patients continue to develop vascular inflammation and complications. This has been termed as “metabolic memory” and believed to be correlated to the epigenetic changes such as chromatin histone lysine methylation/demethylation and gene expression. Villeneuve et al. [56] investigated metabolic memory in type 2 diabetes-derived vascular smooth muscle cells (VSMC), which revealed that these cells retained the atherogenic and inflammatory phenotype even after culturing in vitro. A series of experiments demonstrated protective roles for H3K9me3 and Suv39h1 against the preactivated state of diabetic VSMC [56], suggesting that dysregulation of epigenetic histone modifications may be a major underlying mechanism for metabolic memory and sustained

Fig. 3 Depiction of hyperglycemia-induced epigenetic changes. Hyperglycemia induces epigenetic changes through modulation of enzymes that methylate or demethylate histone proteins. LSD1 is an enzyme that specifically demethylate histones at lysine residue. LSD1 is suppressed in hyperglycemic environment. On the other hand, SET7 involved in the methylation of lysine 4 of histone 3 gets activated in the presence of hyperglycemic conditions. As shown in the figure, the changes in LSD1 and SET7 mobilize transcription factors that bind to p65 promoter and activates NF-κB leading to upregulation of proinflammatory target genes. Increased inflammation is known to promote vascular complications

proinflammatory phenotype of diabetic cells. Similar findings were reported by Reddy et al. [57] using chromatin immunoprecipitation assays and showed that levels of histone H3 lysine 4 dimethylation (H3K4me2), a key chromatin mark associated with active gene expression, were significantly elevated at the promoters of the inflammatory genes such as MCP-1 and IL-6 in db/db VSMCs. Protein levels of lysine-specific demethylase1 (LSD1), a negative regulator of H3K4 methylation, were significantly reduced in db/db VSMCs [57]. In a parallel experiment, treatment of human VSMC with high glucose (25 mmol/L) increased inflammatory genes with concomitant increases in promoter H3K4me2 levels and reduced LSD1 recruitment [57]. Further studies by Li et al. [58] showed that histone H3 lysine 4 methyl transferase, SET7/9, regulates NF-κB -dependent inflammatory genes, such as TNF-α and play key roles in the pathogenesis of inflammatory diseases and diabetes and the metabolic syndrome. These researchers showed that the chromatin histone H3-lysine 4 methyltransferase, SET7/9, is a novel coactivator of NF-κB, suggesting a novel role for SET7/9 in inflammation and diabetes. Almost same time El-Osta et al. [48] carried out series of elegant studies and showed that transient high glucose causes persistent epigenetic changes and altered gene expression during subsequent normoglycemia, demonstrating metabolic memory. Transient hyperglycemia induces persistent mobilization of Set7 to the p65 promoter. Further evidence

of Set7 influence on p65 promoter activity was demonstrated by Set7 knockdown study that showed prevention of glucose-induced up-regulation of p65 and the NF- κ B –dependent genes MCP-1 and VCAM-1 [48]. In a separate study, Miao et al. [59] demonstrated that high glucose increased the transcriptional activity of NF- κ B, which induced TNF- α and Cox2 promoter activity. As shown in Fig. 3, diabetic conditions increase in vivo recruitment of NF- κ B and HATs, as well as histone acetylation at the promoters of inflammatory genes, leading to chromatin remodeling and transcription. Thus, epigenetic changes play an important role in the progression of chronic diseases like diabetes, CVD and NASH [40, 60, 61].

Lack of prediabetes management leads to diabetes

Prediabetic conditions i.e. those with border line glucose and HbA1c, but impaired glucose tolerance and impaired fasting glucose are at higher risks of developing diabetes and eventually CVD [62], since about 70% of them usually develop type 2 diabetes over their lifetime [63]. This is single handedly fueling the diabetes epidemic. According to the U.S. Centers for Disease Control and Prevention, an estimated 79 million Americans, about 35% of the adult population have prediabetes. In addition, about 11% of these people go on to develop full diabetes each year. As many as 53.1 million Americans could develop diabetes by 2025, a 64% increase from 2010. Since prediabetes is a high-risk state for developing diabetes [63], diagnosis and prevention of progression of diabetes in prediabetic individuals appear to be a reasonably good checkpoint to help prevent diabetes progression in these individuals and prevent diabetes-associated pathologies leading to CVD and late-stage diabetes complications (Fig. 4). Indeed, clinical data published [64] and presented at the 2012 American

Fig. 4 High calorie food intake leads to overweight that triggers a series of metabolic derangements, including insulin resistance and impaired glucose tolerance. This sets the stage of prediabetes, which, if not checked appropriately, progresses to full blown diabetes

Diabetes Association, Philadelphia, do suggest that maintaining euglycemia in prediabetics by certain interventions like metformin and changes in life style prevented development of diabetes compared to those who were not on metformin or on regular exercise. Thus, maintaining HbA1c can prevent individuals from developing full blown diabetes. An increase of 1% in HbA1c has been shown to be associated with a 28% increase in risk of death independent of age, cigarette smoking habit, and plasma lipids [25].

Progression of NASH in diabetics

Nonalcoholic fatty liver is the first stage in the progression to steatohepatitis and fibrosis. Several factors may cause NASH progression, including high calorie food intake, weight gain, and adipogenesis [65]. Pathological conditions like diabetes, hyperlipidemia and low-grade inflammation also contribute to the development of NASH. As shown in Fig. 5, diabetes and metabolic derangement together with energy imbalance cause overproduction of lipids in the liver and leads to fatty liver formation [66]. If not checked at this stage, the disease progresses to the next stage (Fig. 6) where inflammation plays an important role together with lipid and glucose-mediated toxicity, miRNA dysbalance [61] and iron overload [67] and produces a pathological condition termed as hepatic steatosis and characterized by fibrosis and liver injury [68, 69]. In some cases, further worsening of the disease occurs as a result of extracellular matrix degradation, remodeling and mitogenesis leading to hepatocellular carcinoma [68]. Diabetes mellitus individuals often have fatty liver leading to non-alcoholic fatty liver disease that develops into non-alcoholic steatohepatitis (NASH) and fibrosis [70], a condition which is becoming

Fig. 5 Type 2 diabetic individuals are at very high risk of developing NAFLD because of fatty liver as a result of dysregulation of lipid metabolism, hyperglycemia-induced lipogenesis, higher AGE-mediated oxidative stress, and inflammation; all contributing to NASH

Progression of Non-alcoholic Steatohepatitis

Fig. 6 Stages of NASH progression. Fatty acid and glucose metabolism are tightly regulated in normal liver. Pathological conditions like dyslipidemia, hyperlipidemia, and diabetes induce oxidative stress, low-grade inflammation, and lipid synthesis collectively set the stage of development of fatty liver. This leads to several pathological conditions including cytokine production, AGE-mediated oxidative stress, and

generation of reactive oxygen species together with miRNA dysbalance and iron overload leading to liver injury and eventually promoting nonalcoholic steatohepatitis. At this stage stellate cells get activated and degradation and remodeling of the extracellular matrix cause liver cirrhosis that progresses to mitogenesis and eventually hepatocellular carcinoma

prevalent in diabetes with no effective therapy. In fact, NAFLD is one of the most common chronic liver disease among those with overweight and diabetes, which is characterized by increased hepatic fat accumulation [71]. Overweight causes NAFLD, which is a risk factor for developing diabetes [66]. Thus, non-alcoholic fatty liver disease and type 2 diabetes coexist and at times synergistically drive adverse effects and contribute to the development of diabetic complications [72]. About 20–30% of diabetic and obesity population have fatty liver and 6% population have NASH [73]. In the United States, 6% children are obese and if the weight gain is not controlled, it eventually results into fatty liver that triggers inflammation and fibrosis (Fig. 6). Individuals with fatty liver have 13-fold higher mortality risk in their 3rd phase of life. Thus, in addition to coronary artery disease, individuals with diabetes also suffer from NASH.

One of the hallmark of diabetes is the elevation of advanced glycation end products (AGEs) [74], formed as a result of non-enzymatic reactions between biomolecules like proteins, reducing sugars, lipids, and nucleic acids [75], and are involved in oxidative stress, vascular inflammation [76, 77], and endothelial dysfunction [78, 79]. A diet containing high AGEs in the presence of high fat induced weight gain and steatohepatitis in CD-1 mice [80], which may represent a model to study the role of AGEs in the pathogenesis of

steatohepatitis [80]. AGE accumulation in the liver causes liver damage and contributes to hepatotoxicity and liver dysfunction as a result of increased inflammation and fibrosis [80]. Indeed, circulating levels of AGEs have been found to be elevated in patients with NAFLD [81] and liver cirrhosis [82].

NASH presents an unmet medical need, since there is no effective treatment despite being the second most sought after pathway for drug discovery after immuno-oncology. Past three decades have seen significant developments for coronary artery disease therapy, but an effective treatment for NASH is still awaiting. If NASH goes untreated, it eventually develops to hepatocellular carcinoma [83] leading to increased sufferings to patients coupled to enormous healthcare costs associated with liver transplant.

Several pathways are being targeted to attenuate progression of NASH, including inhibition of hepatic lipogenesis [84–86], promotion of fatty acid oxidation [87, 88], therapies using antioxidant [89], anti-inflammatory [90], and antifibrotic agents [91]. Other pathways being pursued for NAFLD includes FXR agonists [92] and Bone Morphogenetic Protein (BMP) [93]. Recent findings suggest that miRNA are dysregulated in NAFLD [94, 95] and therefore could serve as a good therapeutic target to treat NAFLD [96]. Indeed, miRNA27a is reported to attenuate NAFLD [97].

cholesterol transport [106, 107]. Additionally, insulin resistant state leads to increased macrophage infiltration and apoptosis, arterial stiffness [108], and modifies vascular tone and smooth muscle cell activation [109]. Increases in arginase activity are also reported in diabetics [110]. Diabetic condition leads to elevated triglyceride-rich lipoproteins (TRL), known to be highly atherogenic, which in turn increases the severity of coronary artery disease [111]. Accumulating experimental evidence suggest that AGE and RAGE are significant contributors to vascular injury [74, 112]. Thus, these unfavorable biologic pathways triggered in diabetic conditions collectively contribute to the progression and worsening of atherosclerotic lesions in the arterial wall (Fig. 7).

elevates AGEs that trigger oxidative modification of proteins, including apolipoprotein A-I, the main protein component of HDL, and elevated inflammation. Both of these processes make HDL dysfunctional leading to impaired removal of cholesterol from the lipid-laden arterial walls. Together, these biologic processes, in diabetic conditions, promote atherosclerosis progression. TXNIP- Thioredoxin Interacting Protein (TXNIP); TRX- Thioredoxin; NLRP3- Nod-like receptor protein; ROS- Reactive oxygen species; AGE- Advanced glycation end-products; oxLDL- Oxidized LDL

The oxidative stress and proinflammatory conditions modify physiological pathways that triggers disease pathophysiology [76].

Among others, HDL, an atheroprotective lipoprotein against developing CVD [115], has been shown to be one of the primary causative factors for increased CVD risks in diabetes in two ways: first HDL concentration in diabetes mellitus is generally lower compared to those with no diabetes [116], and second, HDL function is compromised significantly in hyperglycemic conditions [117, 118], which impairs reverse cholesterol transport (RCT) (Fig. 7) [119], a process that removes proatherogenic cholesterol from the body and inhibits the progression of atherosclerosis and CVD-related complications [115]. Indeed, it was recently shown in multiple animal models that HDL functionality, not HDL concentration, is important in promoting reverse cholesterol transport and attenuation of atherosclerosis [120]. AGEs are known to impair anti-atherogenic property of apoA-I [117] and reverse cholesterol transport [99]. RCT impairment in diabetes occurs as a result of oxidative modification of the main protein component of HDL, apolipoprotein A-I, making HDL dysfunctional [107]. Additionally, AGEs also inhibit SR-BI-mediated reverse cholesterol transport [121]. Thus, AGEs inhibit both ABCA1-dependent [122] and SR-BI-mediated [121] cholesterol efflux. The proinflammatory conditions in diabetes mellitus also contribute to the HDL modifications that abolish normal functioning of HDL [123]. Indeed, in multiple clinical studies reduced RCT as a result of dampened ability of HDL to efflux cholesterol from lipid-laden macrophages has been observed in diabetics [124]. These findings suggest that by controlling diabetes, it is possible to prevent diabetes-associated complications like CVD and NASH. Indeed, new class of anti-diabetes drug, victoza, was shown to be efficacious in diabetes patients leading to reduced cardiovascular events [125] and NASH [126]. This further reinforces the notion that adequate care and prevention of diabetes development together with proper steps at the prediabetic stage definitely help control/prevent progression of diabetes and diabetes-associated complications like CVD and NASH and allow individuals to have healthy and quality life.

Conclusion

In summary, life-style plays a significant role in contributing to metabolic dysregulation through induction of adipogenesis and increased BMI as well as chromatin modification, which over time sets the stage for insulin resistance, impaired glucose metabolism and dyslipidemia. Alteration in the lipid and glucose metabolic pathways leads to the development of type 2 diabetes, which further induces epigenetic changes and contribute to diabetes-related complications. Experimental evidence suggests that obesity and diabetes induce lipogenesis,

oxidative stress, inflammation, and miRNA dysbalance in the liver leading to the progression of nonalcoholic steatohepatitis. Diabetes-induced metabolic derangement together with increased AGEs and low-grade inflammation contribute to increased triglyceride-rich proatherogenic lipoproteins and promotes formation of dysfunctional HDL, leading to increased risk of CVD. Thus, scientific data accumulated over the past three decades confirm the correlation between life-style and diabetes progression, and suggest that changes in life style and management of diabetes are the key steps to help reduce the progression of NASH and CVD risks. In addition, identifying prediabetic individuals and follow-up action appear to be the check-point to prevent the progression of diabetes and diabetes-associated complications.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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