

## Chapter 01

# Increased Risk for Obesity and Diabetes with Neurodegeneration in Developing Countries

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## Abstract

The incidence of global obesity and Type 2 diabetes has increased and is predicted to rise to 30% of the global population. Diet and lifestyle factors are incapable to resolve the increased incidence for obesity and diabetes in various populations of the world. Developing countries have come to the forefront because of the higher diabetic epidemic. The urbanization may possibly provide an explanation for the global diabetic epidemic. In Western countries the metabolic syndrome and non alcoholic fatty liver disease (NAFLD) have reached 30 % of the population and now at present NAFLD afflicts 20% of developing populations. Western diets and sedentary lifestyles cause metabolic disorders in developing countries which may increase neurodegenerative diseases by the disrupted metabolism of xenobiotics in urban populations. In developing countries access to high calorie diets in urban areas down regulate

liver nuclear receptors that are responsible for glucose, lipid and toxicological sensing and interrupt the metabolism of xenobiotics that become toxic to various tissues such as the pancreas, heart, kidney, brain and liver. Xenobiotics in urban areas induce epigenetic changes that involve chromatin remodelling by alterations in transcriptional regulators with modification of histones. Dysfunction of nuclear receptors such as the calorie sensitive sirtuin 1 (Sirt 1) gene involves abnormal nutrient metabolism with insulin resistance, NAFLD, energy balance and circadian rhythm disorders. In obesity and diabetes insulin resistance has been connected to poor xenobiotic metabolism

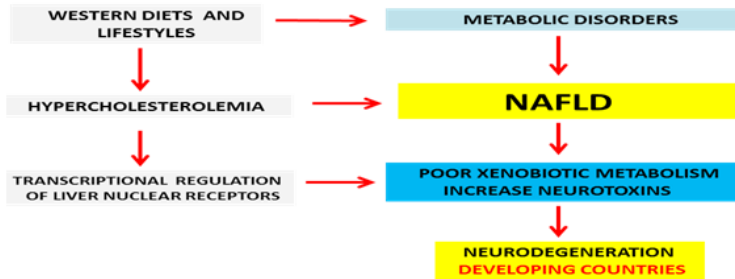
with the toxic affects of increased xenobiotic transport to the brain associated with neurodegeneration. Dietary interventions to increase xenobiotic metabolism are likely to reduce oxidative stress and neuroendocrine disease in developing countries. Prevention programs are an important goal of international health organizations and in developing countries the plans to adapt a healthy diet, active lifestyle and reduced exposure to xenobiotics are important to manage the global epidemic for obesity and diabetes.

## Keywords

Diabetes; Genomic instability; Xenobiotic; Non Alcoholic Fatty Liver Disease; Nuclear Receptors; Developing Countries

## Introduction

Developing countries are important to the understanding of disease processes related to the molecular basis of cell dysfunction and these populations can be used to test the hypothesis of the origins and cause of the metabolic syndrome, accelerated obesity and cardiovascular disease in Western populations. In previous studies disorders such as obesity and diabetes were lower in developing countries and were related to diet, lifestyle and exercise. In developing countries the rapid migration from the rural to urban areas can be used as a model [1,2] and may be an important factor that has accelerated the global diabetic epidemic which has spread to developing countries. The global rise in obesity and severity of diabetes may allow the interpretation of risk factors in developing countries that may possibly explain the cause of early nuclear and cellular dysfunction in Western communities. Interests in the gene environment interactions that change gene expression that affect cellular glucose and lipid metabolism are of considerable interest. Diets high in calories with alcohol consumption in developing countries may affect gene-environment interactions. Developing countries in urban areas may differ from developed countries in relation not only to the calorie content of the diet but also the presence of specific chemicals such as xenobiotics and xenometals. In developing countries (urban areas) access to high calorie diets may downregulate liver nuclear receptors that are responsible for toxicological sensing and interrupt the metabolism of xenobiotics which may rise in the blood plasma with transport to various cells and tissues such as the pancreas, heart, kidney, brain, liver and lungs. The relationship between the food intake and equilibration of xenobiotics or xenometals to various tissues has now become important to the development of insulin resistance and may explain the rise in obesity in developing countries with relevance to the global diabetes epidemic and neurodegeneration (Figure 1) [3-5].



**Figure 1:** Western diets induce the metabolic syndrome, NAFLD and disrupt xenobiotic metabolism.

Developing countries may now consume saturated fat similar to Western countries that may lead to hyperphagia, obesity and diabetes [3,4] being the major disorders in Western communities. In urban areas access to high calorie foods may possibly explain the rise (20%) in non alcoholic fatty liver disease (NAFLD) in developing countries with NAFLD as high as 30% in Western countries [6-8]. The effects of alterations in diets and lifestyle in developing countries possibly promote highly reactive intermediates that are toxic to the cell (nuclear apoptosis) with insulin resistance, abnormal liver lipid metabolism and the development of the metabolic syndrome in these countries. Epigenetic alterations in cells possibly lead to various other diseases such as cardiovascular disease, gall bladder disease, Parkinson's disease (PD) and Alzheimer's disease (AD) that are associated with severity of diabetes and accelerated aging. The global obesity and diabetic epidemic in developing countries require special attention for the understanding of various molecular mechanisms that are involved in the induction or prevention of chronic disease manifestation.

## Increased Global Obesity and Diabetes with the Metabolic Syndrome, NAFLD and Neurodegeneration

The global metabolic syndrome that now includes the under developed countries indicates that the major endocrine disorder is

insulin resistance. The metabolic syndrome and NAFLD have affected 60% of individuals in developed and developing countries [6-8]. These insulin resistant individuals become hypercholesterolemic with hepatic insulin resistance playing a pivotal role in lipoprotein abnormalities. Lipoprotein metabolism is disturbed in these individuals with increased lipid accumulation and excess lipids that are stored in adipose tissue. In obese individuals the classification of obesity is with a body mass index that is greater than 30.0 Kg/m<sup>2</sup>. The liver and its disease progression (NAFLD) with poor lipid metabolism may be responsible for the increased adiposity in obese individuals [9,10] and associated with the induction of the severity of the metabolic syndrome and diabetes in developing countries.

Developing countries are referred to as the countries of Africa, Asia, Latin America and Oceania. In developing countries by 2025 individuals with obesity and diabetes are projected to increase to 115 million and the diabetic epidemic will affect countries such as in Asia and Oceania (Samoa) [11,12]. Extensive literature search by the World Health Organization conducted with terms such as obesity, insulin resistance, the metabolic syndrome, diabetes, dyslipidemia, nutrition and physical activity in developing countries between 1966 to June 2008 indicate that the improved economic situation in these developing countries is associated with increasing prevalence of obesity and the metabolic syndrome in adults and children. The number of people with diabetes is projected to double in developing regions such as Africa, Asia, and India [12,13]. In Asia the diabetic epidemic has escalated and accounts for 60% of the world diabetic population [14]. The diabetic epidemic has been associated with NAFLD in developing countries of Latin America, Asia, India and Africa with prevalence (20- 40 %) similar to developed countries [15-17]. Evidence from various studies indicate that environmental factors are the major determinants of the increasing rates of diabetes with the development of diabetes at a younger age in Asian populations. Rapid urbanization from 20 to 60% has occurred in Africa, India, China and Asia and possibly involved with the large global diabetic population in these developing countries [17-21]. Poor nutrition transition with

increased consumption of energy dense foods and edible oils, sedentary lifestyles, alcohol, polluted environments, poor physical activity and overcrowding possibly contribute to increased social stress that may be responsible for the dramatic increase in these chronic diseases [21-23].

Polluted environments contain chemical compounds foreign to animals and humans are referred to as xenobiotics that include drugs, drug metabolites, and environmental compounds such as pollutants that are not produced by the body. In the environment xenobiotics include synthetic pesticides, herbicides, chemicals and industrial pollutants that pollute the air and water [24-26]. Global disability adjusted life years (DALYS) attributable to air pollution from industry in these developing countries is estimated to be 17 million [24]. Several studies show that air and water environmental pollution in developing countries especially in densely populated urban areas may contribute to at least 20% of chronic diseases and possibly to deaths of millions of people annually in these countries. Alcohol ingestion has been shown to be increased in developing communities that corrupt xenobiotic metabolism [20]. Increased cigarette smoking (tobacco) allow the entry of xenometals such as heavy metals (lead, cadmium, manganese, iron, copper, strontium, rubidium, nickel, zinc, zirconium and chromium) and chemical elements such as (sulfur, chlorine, potassium, calcium and bromine) into the body with toxic effects to the liver and brain [20].

Chronic neurodegenerative diseases associated with Type 2 diabetes have been shown to increase with age in developed countries and recent studies indicate that obesity and diabetes are associated with these neurodegenerative diseases especially those related to AD and PD [27-29]. Studies have concluded that AD is now referred to as Type 3 diabetes and is primarily involved with neurodegeneration and insulin resistance. Neurodegenerative diseases that involve diabetes include ataxia-telangiectasia, Friedreich ataxia, Huntington disease, Prader- Willi syndrome, Werner syndrome, Wolfram syndrome, myotonic dystrophy and Down syndrome/trisomy 21 [29]. In developing countries neurodegenerative disorders such as AD, de-

mentias, epilepsy, PD and acute ischemic stroke stand as emerging public health standards and are closely associated with the increased prevalence in obesity and the metabolic syndrome in these developing communities [28,30,31].

## Gene Environment Interactions induce Epigenetic Alterations in Obesity and Diabetes

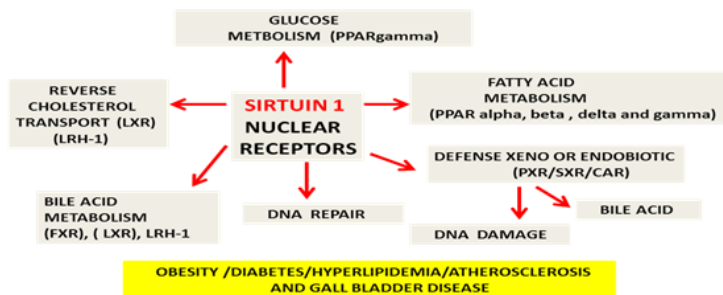
The gene-environment interaction in developing countries indicates that urbanization facilitates increased access to food which leads to induction of epigenetic alterations that are associated with lipid and glucose dyshomeostasis as well as greater adiposity in obese individuals. High calorie diets regulate transcriptional responses with DNA modifications that include DNA methylation, histone tails, chromatin and micro RNA alterations that regulate DNA expression and promote chronic disease susceptibility. Urban environments may contain xenobiotics (soil, water, air) that may also contribute to epigenetic modifications and contribute to the global rise in obesity in these developing countries [32-41].

The alterations in glucose and lipid metabolism in obese individuals involve nuclear receptor dysfunction that promotes liver disease [42-46]. Altered glucose and lipid metabolism in obesity are associated with liver nuclear receptor dysfunction with an increase in lipid storage in adipose tissue. Alterations in the transcriptional regulation of nuclear receptors are responsible for changes in energy and glucose metabolism and involve the peroxisome proliferator-activated receptor gamma (PPAR gamma) and PPARalpha, beta/delta that are responsible for fatty acid, triglyceride, and lipoprotein metabolism [47]. The liver X receptors (LXR)/ liver receptor homolog-1 (LRH-1) is responsible for reverse cholesterol transport, cholesterol absorption and bile acid metabolism regulated by the farnesol X receptor (FXR), LXRs, and LRH-1 receptors. Pregnane X receptor (PXR) and the con-

stitutive androstane receptor (CAR) have endobiotic functions that impact on glucose and lipid metabolism with affects on the metabolic syndrome associated with the pathogenesis of metabolic diseases [48-51]. The nuclear receptor aryl hydrocarbon receptor has also been closely associated with NAFLD [52]. Liver nuclear receptors such as PXR, CAR and xenobiotic sensing nuclear receptor (SXR) are responsible for the detection of foreign toxic substances (xenobiotics) and respond by the expression of cytochrome p 450 (CYP 450) enzymes involved in the defense against xenobiotics (drugs) for rapid clearance by the liver [53,54]. Liver nuclear receptors are involved in the metabolism of nutrients (glucose, fatty acid and cholesterol), bile acid and drug metabolism [54-58] and closely involved in the pathogenesis of chronic diseases such as NAFLD, obesity, diabetes, atherosclerosis, gall bladder disease [59-61] and neurodegeneration.

The gene environment interactions induce epigenetic changes involve alterations in nuclear receptors with chromatin remodelling that are linked to obesity and diabetes. High fat and high cholesterol diets interfere with nuclear receptors and chromatin remodelling that are linked to oxidative stress, insulin resistance and NAFLD. Interest in calorie restriction and transcriptional regulation of nuclear receptors has increased and these receptors are closely involved with insulin resistance. Dietary regulation of the nuclear receptors involves the calorie sensitive anti-aging gene Sirtuin 1 (Sirt 1) that is principally involved in obesity, liver lipid metabolism (NAFLD) and brain neuronal proliferation with close links to the development of AD [61,62]. Sirt1 is a NAD<sup>+</sup> dependent protein deacetylase and is involved in the deacetylation of the nuclear receptors (Figure 2) with its critical involvement in insulin resistance [63,64].





**Figure 2:** Sirtuin 1 regulation of chromatin structure and gene expression with effects on obesity and diabetes.

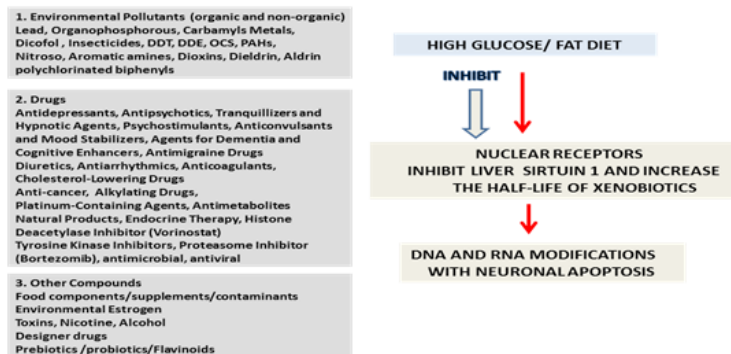
Sirt 1 is involved in metabolic regulation and in the repair of deoxyribonucleic acid (DNA) damage with epigenetic alterations involving histone deacetylation in chromatin [65,66]. Sirt 1 involvement in PXR activation occurs by deacetylation of the PXR liver receptor [67,68] and is linked to protection of DNA by xenobiotics with epigenetic alterations involving histone deacetylation [69-71]. Sirt1 maintains the DNA to prevent gene modification of various genes including CYP 450 enzymes [72] and allows rapid metabolism of xenobiotics that enter the organism. In under developed countries urbanization and Western diet changes involve Sirt 1 dysregulation caused by alterations in transcriptional regulators and modification of chromatin that contribute to endocrine abnormalities such as insulin resistance, NAFLD and energy balance disorders [73-79].

Interests in calorie restriction and neurodegeneration involve Sirt 1 mediated deacetylation of the transcriptional factor FoxO3a that represses Rho-associated protein kinase-1 gene expression and activation of the non amyloidogenic  $\alpha$ -secretase processing of the amyloid precursor protein (APP) with the reduction of amyloid beta ( $A\beta$ ) generation [80]. Environmental changes with dietary consumption of xenobiotics affect chromatin remodelling that regulate gene expression with affects on appetite and hyperphagia that promotes obesity, diabetes and neurodegeneration [81,82].

factors (co-regulator complexes) modify Sirt1 chromatin interactions and nutrient, drug and toxin metabolism [81-83]. Environmental inhibitors modify Sirt1 and its regulators with modifications in chromatin structure and prevent activators of Sirt1 that regulate appetite and food intake [84]. In developing countries movement of populations from rural to urban regions alter Sirt1 and nuclear receptor interactions that act as metabolic and toxicological sensors that allow populations to adapt to environmental changes. High calorie diets down regulate nuclear Sirt 1 activity disrupted xenobiotic or xenometal metabolism that alters gene expression with the acceleration in aging and the development of obesity and diabetes in these populations.

## Metabolic Disorders Affect the Metabolism of Xenobiotics and Increase the Concentration of Neurotoxins

Major threats of xenobiotics such as environmental pollutants (Figure 3) may increase with age in individuals from developing countries [85-89]. These xenobiotics allow induction of various chronic illnesses such as obesity and diabetes by alteration in liver and brain function. The global obesity epidemic (30%) now includes the developing countries (20%) and is possibly connected to the large diabetic population in developing countries with unhealthy diets and poor liver xenobiotic metabolism involved in the severity of diabetes [90-94]. In obesity and diabetes the liver and brain have been found to be diseased with insulin resistance connected to the peripheral organ disease progression [84]. Obese and diabetic individuals have blood brain barrier (BBB) disorders [95] and loss of BBB trafficking of chemicals, xenobiotics or xenometals [96-98] to the brain may increase the risk of neuronal apoptosis with the promotion of neuroendocrine disease and the increased risk for PD in these individuals [96,97-99]. Association between xenobiotics and insulin resistance adds support to the affects of xenobiotics on their receptors CYP 450 in liver and brain cells of obese and diabetic individuals [100-104].



**Figure 3:** Nuclear receptors control xenobiotic metabolism with effects on DNA modification and neuron apoptosis.

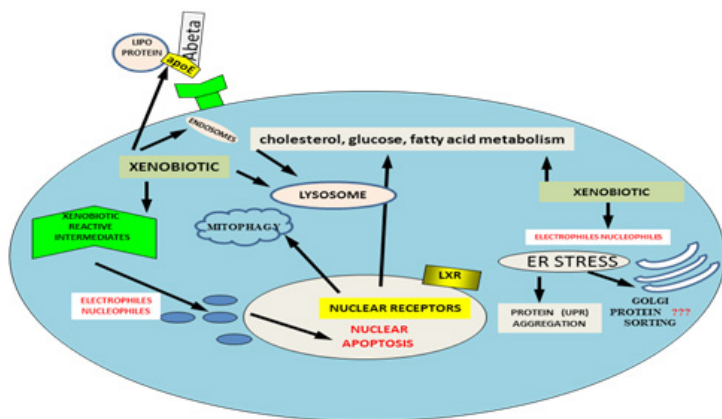
In experimental animals high fat diets were closely associated with disturbances in the suprachiasmatic nucleus and appetite control with the abnormal involvement of Sirt1 in the central control of circadian rhythms [105-111]. Sirt 1's abnormal involvement in food intake and appetite regulation has been associated with the risk for obesity [107,110,111]. The clearance, metabolism and elimination of xenobiotics are controlled by nuclear receptors (Sirt1/PXR) and the circadian regulation of CYP450 enzymes that are involved in xenobiotic and nutrient metabolism [49,112-114]. High calorie diets with lifestyle alterations after relocation to urban areas possibly delays the metabolism of xenobiotics with induction of cardiovascular disease [115-121] metabolic diseases such as obesity and diabetes [11,122] and relevance to drug induced Parkinsonian and neurodegeneration in these countries [123-125].

Accelerated neurodegeneration such as in PD and AD is connected to the diabetic global epidemic with insulin resistance and abnormal peripheral glucose and lipid metabolism. Excess xenobiotics (CNS drugs, CAD drugs, anti-cancer drugs, antimicrobial, antiviral,

compounds) are possibly involved in the molecular mechanisms of neuroendocrine disease that is linked to diabetes, PD and AD. Organic pollutants in the environment are higher in developing countries and the half life of xenobiotics by poor hepatic metabolism is decreased with the increase in NAFLD (20%) and diabetes associated with these under developed countries (Figure 3). Loss of hepatic cholesterol metabolism as associated with NAFLD is closely connected to poor liver A $\beta$  homeostasis with consequences to severe neurodegeneration such as PD and AD. In 60% of individuals in global populations (developed and developing countries) the peripheral sink A $\beta$  hypothesis is absent since NAFLD has increased to nearly half of the world population and ill affects of poor xenobiotic and hepatic A $\beta$  metabolism correlated with toxic affects to various tissues such as the heart and brain [61,62].

Interests in xenobiotic metabolism have escalated recently since xenobiotics are involved in the generation of reactive intermediates that corrupt DNA repair and promote DNA modifications [126-128]. Xenobiotics release reactive electrophiles that are possibly connected to nuclear aggregation and endoplasmic reticulum (ER) stress [129] with protein deposits in cells (Figure 4). The damage to DNA occurring in neuronal cells with xenobiotics is with the formation of DNA adducts, DNA strand breakage and altered DNA function [127,130]. Sirt 1 is closely involved in with chromatin modification and protection of neurons from genotoxic stress with the involvement of DNA repair enzymes and repair of double strand breaks in damaged chromatin structure [131,132]. In liver and brain cells with low Sirt 1 activity electrophiles from xenobiotic metabolism react with micro ribonucleic acid (RNA) [133-135] or by covalent binding to nucleophilic centres in cellular protein and DNA [136-139]. Adduct formation disrupts DNA or protein structure with damage to the nucleus and various subcellular organelles [128,130,140] such as the ER and mitochondria with metabolic alterations. Diets that disrupt Sirt 1's protection of ER stress are also implicated in mitochondrial dysfunction with the essential role of Sirt 1 and nuclear receptors in the maintenance of the mitochondria and their biogenesis [140-143]. Xenobi-

otics promote oxidative stress with the release of radicals that cause chain reactions with the attack on DNA, lipids, proteins and carbohydrates. Xenobiotics generate electrophilic intermediates that involve abnormal protein folding as assessed by quality control mechanisms such as the unfolded protein response and the deposition of unfolded proteins in the ER. As nutrient levels rise Sirt 1 activity falls and xenobiotic oxidative processes rise with protein misfolding connected with insulin resistance in neurodegenerative diseases such as PD and AD.



**Figure 4:** The effects of xenobiotics on nuclear apoptosis and ER stress in obesity and diabetes.

## Unhealthy Diet, Drugs and Lifestyle Induce Chronic Disease and Neurodegeneration

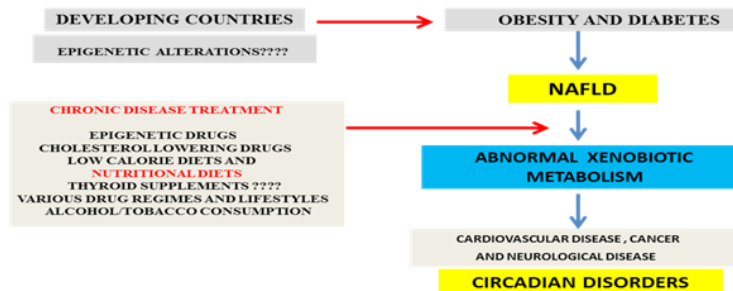
Populations that consume alcohol and tobacco such as that in developing countries may inhibit hepatic nuclear receptors with alterations in metabolic regulation of cholesterol, fatty acids, glucose and toxic chemicals. Alcohol is a Sirt1 inhibitor [144-147] and its consumption may promote hepatic dysfunction such as alcoholic fatty liver with the ill affects on hepatic xenobiotic metabolism that are

now released to various organs in the periphery and brain. Activators of hepatic Sirt 1 are important to prevent chronic diseases with the maintenance of liver nuclear receptors and regulation of nutrient and xenobiotic metabolism [61,62] Foods that contain toxic xenobiotics [148] induce genotoxic stress with chromatin modifications that leads to hepatic DNA damage and NAFLD that threaten the survival of various obese and diabetic individuals [148,149].

Interest in fat consumption (low or high) may require further evaluation and may contain lipophilic xenobiotics. Lipophilic xenobiotics [150,151] such as aldrin and dieldrin may rapidly transport across membranes to various cells and tissues may not be processed by the liver. Gene-environment interactions that lead to changes in diet and appetite affect peripheral gene expression with the development of the metabolic syndrome and possibly involve the excess consumption of lipophilic xenobiotics found in fat (milk) that are toxic to the neurons in the central nervous system. Rapid xenobiotic metabolism is triggered by low calorie diets and poor nutrition leads to abnormal xenobiotic metabolism with significant effects on DNA strand breakage with cell apoptosis. Compounds such as resveratrol (Sirt1 activator) are essential to maintain the DNA repair [152-154] and are involved in inhibition of CYP450 enzymes required for xenobiotic metabolism [155,156].

In developing countries higher environmental organic pollutants can enter the water supply and foods such as vegetables, rice, fruits, meat and dairy products. Consumption of water and food may release xenobiotics that may alter cellular DNA and RNA related to the epigenetic changes in metabolic diseases and neurodegeneration (Figure 5). Food monitoring for xenobiotics and xenometals has become of central interest to prevent chronic diseases and acceleration of aging with the prevention of ingestion of toxic chemicals, xenobiotics and organic pollutants (88-90). In Western communities nutritional diets are of importance to prevent NAFLD and improve hepatic xenobiotic metabolism in these communities. Xenobiotics and its connections with various chronic diseases may involve abnormal xenobiotic biotransformation and their reactions such as oxidation, conjugation

and reduction are important to its rapid metabolism and excretion in bile and urine. Chronic diseases such as gall bladder disease and hypothyroidism has increased with the metabolic syndrome and gall bladder removal now closely related to NAFLD [157,158]. The slow metabolism of xenobiotics in individuals with insulin resistance [159] may lead to dysfunction of the thyroid and hypothyroidism is now involved with the progression to obesity and diabetes [160-162].



**Figure 5:** Nutritional diets and active lifestyle improve xenobiotic metabolism and reduce chronic diseases such as obesity, diabetes and neurodegeneration in developing countries.

Anti-obese drug therapy in obese individuals may be more useful and successful with consumption of selected foods that are very low in xenobiotics, chemicals or xenometals that allowing the the liver to rapidly clear these toxic compounds from the periphery before entering the brain (Figure 5). Anti-steatotic diets and drug treatment may accelerate clearance of liver xenobiotics by improving insulin resistance and expression of CYP450 expression [102-104] in obese or diabetic individuals. Other behavioural factors such as stress and anxiety that affect the circadian rhythm that regulates xenobiotic metabolism have become important to various communities. Nutritional diets (plant versus meat) are designed to maintain the toxicological processing of xenobiotics with the critical role of liver xenobiotic enzymes (CYP450) in their metabolism. Micronutrients, minerals and vitamins such as nicotinamide, riboflavain, niacin, folic acid, vitamin

E, vitamin A are essential for xenobiotic metabolism [113]. Diets that contain appropriate protein quality, carbohydrate and lipid (polyunsaturated) content are essential for xenobiotic metabolism and nutritional deficiency has been closely related to poor xenobiotic metabolism.

## Conclusion

In various regions in developed and underdeveloped countries the incidence of overweight and obesity has been closely connected to the diabetic epidemic. Urbanization in developing countries may possibly provide an explanation for the global diabetic epidemic. The obesity and diabetic epidemic in developing countries require urgent attention to maintain cellular DNA and RNA and reverse epigenetic changes induced by diet and xenobiotics that accelerate insulin resistance, cardiovascular disease and neurodegeneration. Severity of the world wide diabetic epidemic may be controlled by consumption of low calorie nutritional diets that are designed to maintain liver glucose, lipid and xenobiotic metabolism and prevent genotoxic stress that is associated with the increase in the diabetic epidemic and neurodegeneration in developing countries.

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