Drug therapy for obesity with anti-aging genes modification

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Drug Therapy for Obesity with Anti-Aging Genes Modification

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Abstract

Nutritional regulation and drug therapy has been the focus of the current obesity epidemic in various countries in the world. Epigenetics is the major mechanism for the development of insulin resistance and obesity with unhealthy diets, oxidative stress and environmental factors relevant to alterations in gene expression with effects on mitochondrial biogenesis, adipose tissue lipid metabolism and energy expenditure. Anti-aging genes are involved in the regulation of adipogenesis with increased sensitivity to anti-aging gene dysfunction associated with adipocyte-neuron interactions compared to other cells. Unhealthy diets downregulate adipocyte anti-aging genes associated with the development of Non Alcoholic Fatty Liver Disease (NAFLD) with relevance to regulation of drug metabolism and delayed pharmacokinetics in the body. Evaluation by different methods and techniques to quantify and characterize adiposity has been undertaken to obtain a better understanding of adipocyte metabolism in obesity but adipocyte analysis is now required to determine adipose tissue anti-aging gene expression. Effective drug treatment programs cannot be determined in individuals with obesity with defective adipocyte tissue gene expression. New drug development needs to be carefully interpreted in relation to nutritional intake with drug safety concerns/adverse effects relevant to adipogenesis and NAFLD in obesity.

Keywords: Obesity; Metabolism; Drugs; Diet; Anti-aging genes; NAFLD

Introduction

The susceptibility of humans to obesity is far higher compared with other species and in man favours the deposition of fat. Amongst mammals, humans have been reported to have the highest levels of fat than any other species and genes and environmental factors such as exercise, drugs and diets may predispose humans to obesity. In the world obesity has more than doubled since 1980 and in 2014 more than 1.9 billion adults (18 years and older) were overweight with 600 million adults were obese [1]. In the USA obesity trends and rates indicate that more than a third of adults (34.9 percent) were obese as of 2011 to 2012 [2]. More than two-thirds of adults were overweight or obese (68.6 percent) with17 percent of children obese and 31.8 percent were either overweight or obese.

In particular, intra-abdominal adipose tissue referred to as visceral fat has been associated with the metabolic syndrome and obesity. Visceral fat is more metabolically active than peripheral fat with the waist-to-hip ratio that identifies patients with excess visceral adiposity. Women with a waist-to-hip ratio >0.8 and men with a ratio >1.0 are considered to have excess central adiposity that confers risk for developing the metabolic syndrome and Non Alcoholic Fatty Liver Disease (NAFLD). Morbid obesity is classified as a BMI of >35 kg/m² and severe obesity>40 kg/m². Adiposity is the body fat tissue content and its increase is measured by Body Mass Index (BMI). Obese individuals are defined as having a BMI of >30 (BMI = weight in kg/m² [height in m]) whereas overweights are defined as having a BMI from 25 - 30 kg/m² and ideal lean individuals to have a BMI of 25 kg/m². The role of adipose tissue and the induction of obesity early in life are of critical understanding to the development of hyperinsulinemia which may lead to diabetes and other morbid diseases such coronary artery disease and NAFLD [3].

Interests in anti-obese drugs as the major intervention for weight loss has been an important strategy for the treatment of obesity. Drugs that have been developed for the treatment of obesity are either involved in the reduction of energy intake or the increase of energy expenditure and their beneficial effects may include improvements in glycemic control or psychiatric illness. Interests in the use of obesity drugs have increased since safety and use of the drugs for continued weight loss (reduced visceral fat stores) have become of concern to medical authorities in Western communities [4-9]. Anti-obesity drugs that improve insulin resistance, dyslipidemia and the metabolic syndrome have not been appropriate to lifestyles, diet and health conditions and drug effectiveness have been variable without weight loss. Long term treatment of obesity with the use of anti-obese drugs particularly centrally active agents has not been achieved with safety concerns and withdrawals due to adverse effects that were never predicted from clinical trials and drug development. Removal of several of these drugs from the market has allowed the introduction of other drugs such as gut based hormone treatments which target many pathways involved in the regulation of energy balance (Contrave TM or Empatic TM).

Epigenetic modifications involve anti-aging genes with increased risk for adipogenesis

The understanding of genetic factors involved in the risk for obesity has identified genes that are closely linked to obesity related
down regulation of these anti-aging genes via its role as a NAD+
derived deacetylase and p53 transcriptional dysregulation of these
genes [18,20]. Bacterial Lipopolysaccharides (LPS) have been shown
to induce insulin resistance, adipocyte dysfunction with transport of
LPS lipoproteins to adipose tissue [39-41]. LPS has been shown to
repress Sirt 1 by defective transcriptional regulation [42] and its role
in obesity has been clearly documented [39-41]. Diets that are high
in fat stimulate LPS absorption [42] and LPS in dietary lipoproteins
induce NAFLD and obesity. The role of Sirt 1 and LPS with relevance
to adipocyte dysfunction is also relevant to neurodegenerative
diseases such as Alzheimer’s disease and Parkinson’s disease [43-
45]. LPS interferes with Sirt 1 regulation of neuropeptide Y [20] with
relevance to the hypothalamus and adipose tissue connections (Figure
1) associated with disturbed energy metabolism in the adipose tissue
[46,47].

Methods of visceral fat measurement, adipocyte analysis
and drug treatment programs

The critical evaluation of different methods and techniques to
quantify and characterize adiposity has been discussed to obtain a
better understanding of fat metabolism in obesity. These methods
include anthropometric techniques, bioelectrical impedance
analysis, dual energy X-ray absorptiometry, and air displacement
plethysmography, Ultrasound, CT and MRI. The quantitative
assessment of intra-abdominal adipose tissue is by CT and MRI and
represents a direct method of assessing visceral fat deposition in both
adult with other methods of visceral fat assessment associated with
imprecision or poor reliability [48]. In the global obesity epidemic a
direct diagnosis of adipocyte dysfunction needs to be made early in
time to determine that adipogenesis relevant to defective adipocyte
and fat metabolism has advanced that cannot be characterized by methods
of visceral fat assessment. Analysis of adipocytes by flow cytometry
as well as isolation of adipocytes by flow sorting (Figure 1) has been
completed [49,50] that now can allow anti-aging gene expression
analysis of adipocytes [51] from individuals at various ages.

In adipose tissue gene expression profiles of Klotho, p66Shc
(longevity protein) and Fork head box proteins (FOXO1/ FOXO3a)
have been completed and indicate down regulation of these genes
are related to mitochondrial apoptosis, adipogenesis and adipocyte
differentiation [26-38]. The anti-aging gene Sirt 1 is central to the
down regulation of these anti-aging genes via its role as a NAD+
metabolism, energy expenditure, taste and appetite of the organism.

The search for specific genes that are sensitive to nutritional
regulation, oxidative stress, inflammation, endocrine disease, lipid/
glucose metabolism and insulin resistance has been the focus of the
current obesity epidemic in various developed countries. Epigenetics
is now considered as an important mechanism for the development
of obesity and can result from changes in cellular chromatin structure
without alterations in DNA sequence, including DNA methylation,
histone modifications and chromatin remodelling. Epigenetic modifications in adipocytes are more sensitive compared to other cells
and are altered by unhealthy diets with increased oxidative stress or
environmental factors that have the ability to change adipocyte gene
expression with effects on mitochondrial apoptosis, lipid metabolism
and energy expenditure. Epigenetic modifications that involve the
anti-aging genes in the adipose tissue have become important and
are closely involved with adiponecin release associated with the
regulation of hepatic lipid metabolism and the induction of NAFLD
[18].

The increased susceptibility to fat deposition in humans is far
higher compared with other species and indicate that in man the
susceptibility to down regulation of the anti-aging genes by Western
diets and lifestyle alterations (stress, heavy workloads) that alter
the metabolism of dietary fat in the liver with the development of
adipogenesis [19]. The connections between the anti-aging gene
Sirtuin 1 (Sirt 1) and other anti-aging genes such as Klotho, p66Shc
(longevity protein) and Fork head box proteins (FOXO1/ FOXO3a)
have been associated with appetite regulation, mitochondrial
apoptosis and the accelerated aging process with these anti-aging
genes involved in the regulation of glucose, lipid and amyloid beta
metabolism that are important to NAFLD and obesity [20]. These
anti-aging genes have become important and may supersedethe
effects of DNA methylation (epigenetic), genes and transcription
factors important to the world-wide obesity epidemic with increased
risk for adiposity. The involvement of the anti-aging gene Sirt 1 in
the regulation of adipogenesis has been shown [21-23] with adipocyte
dysfunction associated with excess transfer of fat to liver with NAFLD
[18,24,25] (Figure 1).

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Long term treatment of obesity with the use of anti-obese drugs may not have been successful with over nutrition and LPS involved in the corruption of effective anti-obese drug treatment programs [42] and withdrawals due to these adverse effects were never predicted from clinical trials and drug development. The anti-aging gene expression (down regulation) of adipocytes may indicate the presence of LPS or Sirt 1 inhibitors in adipose tissues. The consumption of Western diets/ alcohol completely downregulate Sirt 1 with adipocyte isolation and analysis required for early diagnosis of adipogenesis defects. Effective anti-obese drug treatment programs cannot be determined in individuals in the developing/developed world until plasma analysis of LPS, Sirt 1 inhibitors [52], fatty acids such as butyric acid, palmitic acid (Sirt 1 inhibitors) [3,20] and xenobiotics [53] can be determined to assess effect on adipose tissue gene expression in man. The effective anti-obese drugs in clinical trials and new drug development need to be carefully interpreted in relation to safety concerns/adverse effects with relevance to Sirt 1 inhibitors that may be routinely consumed in various diets by obese individuals.

Conclusion

In global communities humans are more susceptible to adiposity compared with other species with the increased development of overweight individuals, NAFLD and obesity. Drugs that improve insulin resistance, dyslipidemia and the metabolic syndrome with long term treatment have not been successful with removal of various anti-obese drugs from the market. Defective anti-aging genes are linked to mitochondrial apoptosis in obesity and indicate that these genes are associated with defective hepatic drug clearance and metabolism. Liposarpirates from obese individuals allow assessment of anti-aging genes relevant to mitochondrial biogenesis and effective drug therapy will be determined by non consumption of inhibitors of anti-aging genes (drugs) and consumption of healthy low calorie diets that activate adipocyte anti-aging genes.

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