A new challenge for diabetologists and geriatricians!

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SUMMARY
The “Société Française de Gériatrie et Gérontologie” (SFGG) and “Association de Langue Française pour l’Étude du Diabète et des Maladies Métaboliques” (ALFEDIAM) have decided to join their efforts in actions to improve the management and treatment of the elderly diabetic patients. New knowledge brought by the fundamental research in the domains of longevity genes made possible to discover genetic ways, like IGF-1 (insulin-like growth factor 1) which play a regulating role between adequacy of the external food availabilities and nutritional body needs. Others discovery in the field of the epigenetic regulation of the nutrition have consequences on pathology such as the metabolic syndrome. New therapeutic prospects and a better definition of the clinical feature will allow better prevention and management in prediabetic patients.

Key-words: Diabetes · Aging · Longevity assurance gene · IGF-1 · Epigenetic · Metabolic syndrome.

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RÉSUMÉ
Un nouveau challenge pour les diabétologues et les gériatres !
La Société Française de Gériatrie et Gérontologie (SFGG) et l’Association de Langue Française pour l’Étude du Diabète et des Maladies Métaboliques (ALFEDIAM) ont décidé de joindre leurs efforts pour améliorer la prise en charge et le traitement des patients diabétiques âgés. Les connaissances nouvelles apportées par la recherche fondamentale dans le domaine des gènes de longévité ont permis de découvrir des voies génétiques, telle que l’IGF-1 (insulin-like growth factor 1), qui jouent un rôle régulateur entre l’adéquation des disponibilités alimentaires externes et les besoins corporels nutritionnels. D’autres découvertes dans le domaine de la régulation épigénétique de la nutrition ont des conséquences sur des pathologies comme le syndrome métabolique. De nouvelles perspectives thérapeutiques et une meilleure définition du tableau clinique devraient permettre une meilleure prévention et prise en charge des patients âgés pré-diabétiques.

Mots-clés : Diabète · Vieillissement · Gène d’assurance longévité · IGF-1 · Épigénétique · Syndrome métabolique.
The Société Française de Gériatricie et Gérontologie (SFGG) and the Association de Langue Française pour l’Étude du Diabète et des Maladies Métaboliques (ALFEDIAM), also implied by the problem of the treatment of the diabetes of the elderly subject, have decided to join their efforts. They set up a working group on this problem. The geriatric step is based on a stronger gerontologic research from day to day. One of the axes of this fundamental research, which is in full rise currently, is the comprehension of the molecular mechanisms of longevity that has its natural limitation in the aging process. A second axe is the gene imprinting that brings new therapeutic perspectives for the metabolic syndrome.

Aging and longevity genes

Recent data have suggested that, during the Evolution, aging is caused by accumulation of somatic damage, which can be retarded by somatic maintenance systems [1]. Emerging evidence points toward the existence of a universal genetic regulatory network that controls longevity and aging rate through the manipulation of wear and tear processes and cellular defense systems. Three types of genes have been postulated [2].

Late deleterious aging genes [3] originate in accidental germ line mutations, which are neutral at early age but start exerting their adverse effects at later ages. In humans, late deleterious aging genes could explain certain age-related diseases, such as familial forms of Alzheimer’s disease and Huntington’s disease.

Antagonist pleiotropic aging genes [4], on the other hand, involves the concept of accidental mutations with some beneficial effect early in life and adverse effects later. They are relatively few. The original example is enhanced calcium deposition in bones, the late effects of which could be the depositions of calcium in arterial walls. Another example would be the role of p53-dependent apoptosis in preventing cancer and possibly, causing aging [5].

Longevity assurance genes [2] are adaptation genes affecting endocrine signaling, stress response, metabolism, and telomeres and all of them can increase the life span of model organisms. These mutations have revealed evolutionarily conserved pathways and are promoted through the manipulation of metabolism and resistance to oxidative stress. The best understood of these genes is the insulin/IGF-1 pathway which influence the lifespan in worms, flies and mammals. Insulin/IGF-1 signaling appears to be only one step in a signaling cascade that affects life span. A signaling role of adipose tissue and FOXO (Forkhead box O) activity extends the life span of flies. Down stream genes have been now been identified: antioxidant genes such superoxide dismutase, metallothionine, catalase, and glutathione S-reductase ; metabolic genes including apolipoprotein genes, glyoxylates-cycle genes, and genes involved in amino acid turnover, and chaperones, particularly small heat shock proteins genes and anti-bacterial genes.

Those data rise several questions on the role of IGF-1 (insulin-like growth factor 1), dietary restriction, vicious cycle, mitochondrial connection, epigenetic modification and fat regulation.

Insulin/IGF-1 paradoxes

Insulin and IGF-1 are clearly beneficial [6]. They are anabolic hormones and that promote food storage and growth. Yet, reducing the activities of these hormones also seems beneficial since it lengths life span. How can we explain this apparent paradox? The finding that low insulin/IGF-1 signaling activates stress resistance genes provides a possible answer: most likely low signaling levels shift cells from states of growth, which may not equip them for long-term survival, to states of maintenance, which do equip them for long-term survival, thereby delaying aging. It also seems paradoxical that reduced insulin/IGF-1 signaling extends life span, but that insulin resistance leads to type 2 diabetes. The basis for this paradox is not known, but there are some interesting issues to consider. Firstly, the specific perturbation is important: whereas loss of the insulin receptor in adipose tissue extends mouse life span, its loss in the liver cause diabetes [7]. Presumably, this is because adipose tissue lacking the insulin receptor produces longevity signals, whereas liver lacking the insulin receptor does not. Secondly, in worms and flies, reducing the activity levels of insulin-like peptides, as reducing receptor activity, can extend life span [8]. These findings do not seem paradoxical because in mammals, low circulating insulin levels are generally associated with insulin sensitivity and longevity. Thus, the real paradox is why, in mammals, low insulin levels are associated with good health, but low insulin responsiveness with poor health? It seems that insulin-resistant cells on the path to type 2 diabetes have fundamentally different regulatory state from that of normal cells exposed to low levels of circulating insulin. Insulin-resistant prediabetic cells signal the pancreas to overproduce insulin, thereby possibly creating an insulin gain-of-function situation. In contrast, insulin-sensitive cells in animals with low levels of circulating insulin do not trigger insulin secretion. Perhaps these cells instead produce downstream longevity signals. Small dogs live much longer than large dogs, possibly because they have lower levels of IGF-1 [9].

Dietary restriction

Dietary restriction extends life span and postpones age-related diseases in many animals, including yeast, worms, flies, rodents, and possibly primates. It is not clear yet whether the insulin/IGF-1 pathway mediates the diet restriction in mice and is independent of any fat storage. Dietary restriction studies have demonstrated that this mechanism is related to the chromatin activation of the histone deacetylase Sir2 in yeast, worms, flies and in mammals (human ortholog: SirT1). SirT1 deacetylates FOXO, which in turn shift
 FOXO target selection toward stress-response genes. Interestingly, increased SirT1 activity promotes fat mobilization by inhibiting activity of the fat regulator transcription factor PPARγ. The antidiabetic thiazolidinediones, which activate PPARγ and increase fat level, increase insulin sensitivity and induce beneficial health effects [10].

Molecular mechanism of the vicious cycle

Surges in blood glucose will activate beta-cells to produce insulin acutely, which over the long term can lead to beta-cell proliferation and ultimately failure. Insulin signals white adipose tissue (WAT) to store fat as triglycerides. Then, this influences the level of hormones produced by white fat cells (increase leptin and a decrease in adiponectin) [11]. The hormonal changes, in turn, can influence the insulin sensitivity of metabolic tissues, which respond to hormones. Notably, since adiponectin is known to increase sensitivity to insulin in metabolic tissues, its decrease can lead to insulin resistance, which would further exacerbate the rise in blood glucose. This vicious cycle may be central in many case of type 2 diabetes.

Mitochondrial connection

Mitochondrial mutations that increase life span have been demonstrated as two respiratory longevity chains. One due to the shift from fermentation to oxidative respiration extends life span of yeast [12]. The other is based on mutations affecting respiratory-chain components, at least some may produce this by decreasing ROS (reactive oxygen species) level. To be effective this inhibition of the respiration must start early in life because it undergoes a regulated response that subsequently increase life span [13].

Epigenetic changes hypothesis

Recent converging data support the hypothesis that obesity, type 2 diabetes, cardiovascular diseases and metabolic syndrome could be the consequence of imbalanced diets on epigenetic processes of programming during life span and between generations [14]. In addition to “thrifty genotype” inheritance, individuals with obesity, type 2 diabetes and metabolic syndrome with an increased risk of cardiovascular diseases have suffered improper epigenetic programming during their fetal/postnatal development due to maternal inadequate nutrition and metabolic disturbances and also persistent during their life time. Those epigenetic changes are associated with DNA methylation and histone modifications leading to chromatin remodeling and regulation of gene expression during a narrow window in pre- and postnatal development. The susceptibility of epigenetic mechanisms controlling gene expression to environmental influences due to their inherent malleability, emphasizing also the participation of transposable elements and the potential role of imprinted genes during critical time windows in epigenetic programming, from the very beginning of development, throughout life. To illustrate this imprinting, protein restriction during gestation increases the rate of pancreatic apoptosis in the offspring rats. This leads to a smaller mass of pancreatic beta-cells and disturbs the development of the endocrine pancreas in the next generation. Similarly, a high-carbohydrate diet in neonatal rats immediately induces hyperinsulinemia, which persists into adulthood without further nutritional stimulus. And then, start a vicious cycle. One of the determinants of placental size is the imprinted gene igf2, which encodes the IGF-2 protein. It regulates development of the diffusion permeability properties of the mammalian placenta.

Fat regulation

There is increasing evidence that mammalian aging is regulated in part by fat storage. WAT affords mammals an opportunity to sense diet and send appropriate signals to coordinate aging in all organs. WAT stores fat as triglycerides when food is abundant. When food is scarce, as in CR animals, cells shed their fat and animals are very lean. WAT is also an endocrine tissue and secretes hormones such as leptin and adiponectin [15]. WAT can sense whether food is abundant or scare and exert organismal effects through the level of hormones it secretes. Even if WAT mass does not directly control life span per se, it likely mediates many age-associated metabolic disorders such as type 2 diabetes or dyslipidemia which can in turn decrease the period of life. A crosstalk exists between WAT, metabolic tissue (muscle and liver) and pancreatic beta-cells, which produce insulin.

Conclusion

The modern approach for diabetologists and geriatricians, in the light of the new genes and mechanisms involved in longevity and aging, will help toward a better early detection of prediabetes in elderly subjects. The knowledge of those molecular mechanisms, will improve and permit to better define elderly subjects who need prevention and treatment. The clinical research must found new molecular biomarkers of the prediabetic stage, more accurate than patients overweight and fat mass evolution. A better clinical picture will be obtain also by collecting information on the full history of maternal obesity of their patients, and far more important, the nutritional epigenetic status during pregnancy and adulthood [14]. Is the insulin resistance related to a dysregulation and decrease of adiponectin? But also by permitting new drugs and new therapeutic approaches, like glucocorticoid inactivation [16], working together with diet and exercise that has been proved to delay onset of type 2 diabetes [17-19].

A new dialogue between geriatricians and diabetologists is starting aimed to a better treatment and share of responsibilities in the management of diabetes in aged subjects!
References