Brief Communication

Newer antidiabetic drugs and calorie restriction mimicry

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ABSTRACT

De-acceleration of aging and delayed development of age-related morbidity accompanies the restriction of calories (without malnutrition) in laboratory mice, nematodes, yeast, fish, and dogs. Recent results from long-term longitudinal studies conducted on primates have suggested longevity benefits of a 30% restriction of calories in rhesus monkeys as well. Among calorie restricted rhesus monkeys one of the mechanisms for the improvement in lifespan was the reduction in the development of glucose intolerance and cardiovascular disease. Although there are no comparable human studies, it is likely that metabolic and longevity benefits will accompany a reduction in calories in humans as well. However, considering the difficulties in getting healthy adults to limit food intake science has focused on understanding the biochemical processes that accompany calorie restriction (CR) to formulate drugs that would mimic the effects of CR without the need to actually restrict calories. Drugs in this emerging therapeutic field are called CR mimetics. Some of the currently used anti-diabetic agents may have some CR mimetic like effects. This review focuses on the CR mimetic properties of the currently available anti-diabetic agents.

Key words: Alpha-glucosidase inhibitors, canagliflozin, dapagliflozin, dipeptidyl peptidase-4 inhibitors, exenatide, exenatide QW, glucagon like peptide-1 receptor agonists inhibitors, liraglutide, metformin, pioglitazone, sodium glucose co-transporter 2

Introduction

"*Hara hachi bu*." "Eat until you are 80% full" [Japanese saying]

The ultimate aim of treating diabetes is to improve both quantity and quality of life. Current diabetes research has focused on cardiovascular outcomes as a marker for safety and efficacy of a drug in the treatment of diabetes. While this is rational, keeping in mind that cardiovascular disease is the main cause of mortality in persons with diabetes, it is at best, a surrogate marker for measuring longevity of life.

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On the other hand, the science of gerontology has made rapid advances in recent years, and evidence is now available that the lifespan of nonhuman primates (monkeys) can effectively be increased by a very "simple" intervention. Calorie restriction (CR) implies a decrease in the amount of total calories consumed (compared to recorded previous intake or to intake in comparable animals of the same species, age, sex, and built) with any malnutrition. Till recently, CR was known to prolong the lifespan of various organisms, including unicellular microbes', nematodes, mice and rats. It was uncertain, however, whether similar effects would be noted in humans.[1] Recent observations from primate studies have been very encouraging, and some promising parallels can be drawn to humans.

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Calorie Restriction and Longevity

In studies undertaken at Cornell University over 70 years back it was noted that laboratory mice that were fed 30–50% less food than mice that ate *ad libitum* tended to live longer in proportion to the degree of CR undertaken.[2] Studies in many other species including yeasts, houseflies, fish, and dogs suggested restricting calories without malnutrition led to a deceleration in the aging process leading to an increase in the median and the maximum age span in calorie-restricted animals.[1]

To understand the effects of CR on nonhuman primates' two large cohorts of rhesus monkeys were randomized to 30% CR in the later part of the 80's. The first cohort was randomized in 1987 at the National Institute of Aging[3] and the second cohort at the University of Wisconsin in 1989.[4] As rhesus monkeys have an average lifespan of 27–28 years and a maximum lifespan of 40 years these studies would need over three decades of observation to make a meaningful interpretation of longevity data. Both these studies recently reported their interim findings. The first report from the University of Wisconsin clearly documents distinct survival advantages of CR in rhesus monkeys. When instituted in adult (age 7–14 years) rhesus monkeys, (median survival roughly 25 years of age) CR was able to reduce age-related death ($P = 0.007$), as well as all deaths, and increase survival ($P = 0.001$), in treated monkeys, as compared to controls. The hazard ratio for age-related deaths and all deaths was 2.89 (1.34–6.25) and 1.78 (1.04–3.04), respectively in control animals as compared to CR-treated monkeys. The mean lifespan in the CR group was 26.23 (1.12 years) as compared to 24.73 (0.83 years) in the control arm.[4] The publication of this data confirms previous understanding, which states that CR is one of the most robust ways of enhancing lifespan. It also strengthens the applicability of animal data to human populations.

Calorie Restriction and Diabetes

How does this information impact our current diabetes care? Diabetes is a complex multi-systemic metabolic disorder, which adversely impacts life expectancy. The average lifespan of a person with diabetes is about one decade less than that of a euglycemic peer. This calls for the development of intervention which is able to improve life expectancy in persons with diabetes.

In rhesus monkeys unsurprisingly one of the most potent mechanisms of longevity was the reduction of cardiovascular risk factors and glucose intolerance in calorie-restricted monkeys. In the University of Wisconsin cohort, none of the individual calories restricted animals developed any degree of glucose impairment at the time of the interim analysis in contrast with the control monkeys who developed diabetes in a fairly good number.[4] The animal data suggests the long-term CR in adult animals is a potent way to prevent the development of glucose impairment.

There are no comparable human studies with CR. Type 2 diabetes mellitus in humans is currently described as a progressive disease with a pathophysiology that involves over eight different organ systems very elegantly explained by DeFronzo as the "ominous octet" in a lecture at the American Diabetes Association (ADA) in 2009.[5] However, this understanding of disease does not really give a valid explanation to the reversibility and induction of normal glucose tolerance in patients with type 2 diabetes who undergo bariatric surgery. The improvements in glucose control happen within a few days after surgery much before there is any significant reduction in body weight.[6] There are many explanations offered for early improvement in glucose tolerance like changes in gut hormone profile, changes in gut bacteria, etc., Both these overlook the most logical explanation for the phenomenon which is an acute profound decrease in calorie intake.

This CR hypothesis was tested in patients with new diagnosis of type 2 diabetes in a small study of 11 patients. During the 8 weeks, study patients with Type 2 diabetes were confined to a 600 calorie diet. All patients with diabetes had a reversal of glucose intolerance at the end of 8 weeks. The normalization of blood glucose happened with 7 days of CR and was accompanied by a 30% reduction in hepatic fat and normalization of hepatic insulin sensitivity. Interesting over the 8 weeks period, there was improvements in beta cell function in addition to changes in the liver. The first phase insulin response tested by a stepped glucose and arginine infusion (the gold standard) in calorie restricted patients was indistinguishable from those of age-matched nondiabetic controls at the end of 8 weeks. A decrease in pancreatic fat content was noted in the same period and a hypothesis that improvements in insulin secretion mirror decrease in pancreatic/islet fat has been suggested.[7]

Calorie Restriction Mimetics

Even if science came up with irrefutable evidence that a 30–40% CR leads to improved mortality and morbidity especially with regards to glucose intolerance and other cardiac risk factors the question to be asked is: Would we do it or, more importantly, could we do it? Considering the

difficulties in getting patients to comply with usual lifestyle instructions the success of long-term CR in humans appear rather bleak.

With this background, it is unsurprising that CR mimetics (CRMs) have been identified as a field for active research. CRMs are defined as any intervention that can evoke similar effects on aging, health, and lifespan, similar to those of CR. One may consider that appetite suppressants like glucagon like peptide-1 receptor agonists (GLP1RAs), calorie wasting drugs like sodium glucose co-transporter 2 inhibitors (SGLT2i), and bariatric surgery, qualify as CRMs. Other authors, however, propose four characteristics necessary to label a drug as a CRM. A CRM mimics the metabolic, hormonal and physiological effects of CR; does not significantly reduce long-term food intake; activates stress response pathways observed in CR and provides protection against a variety of stressors; and leads to a reduction of age-related disease and maintenance of function.[8]

In simpler words, a CRM should mimic the mechanism of action, effects, and long-term outcome noted with CR, without actually causing CR or lack of food intake [Table 1]. Proposed mechanisms by which these drugs mimic CR are summarized in Table 2.

Table 1: Characteristics of a true calorie restriction mimetic

Mechanism of action mimics that of CR
Metabolic, endocrine, and physiological effects mimic those of CR
Activation of stress pathways as is observed with CR
Protection against a variety of stressors as is observed with CR
Improvement in age-related function and longevity as observed with CR
Reduction in age-related disease as observed with CR
No long-term reduction in food/calorie intake

CR: Calorie restriction

Table 2: Proposed mechanisms of action of calorie restriction

Reduced oxidative stress and damage
Reduced glycation of macromolecules
Reduced DNA damage and increased repair
Reduced inflammation and autoimmunity
Increased mitochondrial efficiency
Reduced damage to cellular components
Autophagic proteolysis of damaged cells
Enhanced maintenance of age-related patterns of gene expression
Enhanced protection against stress (hormesis)

Table 3: Potential calorie restriction mimetic glucose lowering drugs

Biguanides: Metformin
Thiazolidinediones: Pioglitazone
Alpha-glucosidase inhibitors
Glucagon-like peptide-1 receptor 2 inhibitors
Sodium glucose co-transporter 2 inhibitors

Calorie Restriction Mimicry of Anti-diabetic Drugs

Let us now assess the currently available anti-diabetes therapies against this benchmark of a CRM. Of the various glucose-lowering drugs, four classes: Insulin sensitizers (pioglitazone, metformin), the glucosidase inhibitors (AGIs), GLP1RA s, and SGLT2i, may be considered as CRMs in a broad sense [Table 3].

A lower level of circulating insulin appears to be an important mechanism of longevity with CR. Hence, all compounds that improve insulin sensitivity have the potential to act like a CRM and improve longevity. Metformin is the most well studied anti-diabetic CRM, which acts by inhibiting mitochondrial enzymes and activating the AMP-activated protein kinase (AMPK). Up-regulation of AMPK appears to increase lifespan in a variety of organisms. The effects on longevity are likely mediated by changes in mitochondrial metabolism and increase in activity of sirtuin and mammalian target of rapamycin signaling pathways which are all tightly linked to CR and promotion of longevity.[9] Retrospective studies have suggested improved all-cause survival in patients with type 2 diabetes and cardiovascular disease prescribed metformin.[10,11] There are suggestions that patients on metformin have decreased the incidence of some malignancies, in particular, breast malignancies in women. Pioglitazone, too, has effects similar to metformin on the AMPK system, thought it acts predominantly via the peroxisome proliferator-activated receptor gamma receptors.[12]

AGIs are a class of drugs which acts by reducing absorption of triglycerides from the gastrointestinal tract. They do not markedly reduce appetite but are able to reduce body weight and improve cardiovascular outcomes. Thought AGIs are not known to act upon AMPK, they share many properties with metformin, including the ability to enhance incretin effect without causing hyperinsulinemia.[13] Thus, AGIs do seem to fit the definition of CRMs.

GLP1RA are an injectable class of glucose-lowering drugs which are also approved for use in obesity. While they do suppress appetite, which means that they are calorie restrictors, their effect on weight reduction is much more than can be explained by a reduction in food intake.[14] Liraglutide is known to inhibit AMPK in the hypothalamus, causing satiety, and browning of white adipose tissue;[15] as well as in the pancreatic beta-cells, leading to improved beta-cell survival.[16] This mechanism of action supports a

CRM-based mode of action for GLP1RA. This class of drugs, therefore, can accurately be called combined CR and CRMs.

Similar to GLP1RA, the dapagliflozin, dipeptidyl peptidase-4 inhibitors (DPP4i) also work by increasing endogenous incretin levels, though to a lower degree. DPP4i are appetite and weight neutral. Some evidence is available regarding the action of DPP4i on adiponectin, which is an AMPK activator.[17] By indirect means, therefore, DPP4i may be considered CRMs.

A new class of drugs, the SGLT2i, deserves attention for its unique mode of action. By promoting glucuresis, it reduces the burden of hyperglycemia in the circulation.[18] It can be argued, and then, that SGLT2i are a true CRM. SGLT2i reduces insulin levels, corrects renal hyperfiltration and weight loss; does not reduce appetite, and activate stress responses pathways including those of glucagon secretion and the tubuloglomerular feedback. Current data suggest that the drugs help improve cardiovascular health and survival. While no research is available to demonstrate the direct effect of SGLT2i on AMPK, it is possible that they may work indirectly via an increase in adiponectin.

Clinical Implications

The clinical implications of this train of thought are significant. Glucose lowering drugs may have a CRM action on the body. While this is certainly helpful in persons who are obese or have "maladaptive anabolism" or multiple components of metabolic syndrome, it may be deleterious in others. CRM may worsen health in persons who are cachexic, have minimal insulin reserves, are calorie-deprived, or have malnutrition. Such patients should ideally receive insulin as is mentioned in modern guidelines. Metformin, too, is not an ideal choice for such persons.

Prescription of AGIs to a person who is already following a low-fat diet will not be of much use, and adding SGLT2i to a carbohydrate-deprived, energy-malnourished person may be inappropriate. CRM glucose-lowering drugs will benefit lean and overweight/obese persons provided their diet is adequate, and they do not exhibit signs of cachexia, extreme insulin deficiency, or enhanced insulin requirement. CRM drugs will also be strongly indicated in person with evidence of insulin resistance, in the form of central obesity, acanthosis nigricans, skin tags, nonalcoholic fatty liver disease, and polycystic ovary syndrome. Yet other robust indications would be a person who is unable to control their appetite and those who are unable to exercise (as exercise is also an AMPK activator).

Whether the use of CRM drugs in diabetes will help improve the longevity of patients is a topic for debate. There are outcome studies which demonstrate prolonged survival in patients randomized to metformin, and acarbose. Cardiovascular studies presented recently at this year's annual meeting of the ADA have shown no adverse effects with lixisenatide and sitagliptin.[19,20] However, much more work is required to map the full extent of effects of CRMs in diabetes management.

An old Japanese saying states; eight parts of the food in your stomach are for you; the other two are for your doctor. By using CRM glucose-lowering drugs appropriately, perhaps, we can ensure that all ten parts of the food that is consumed are able to benefit the person with diabetes.

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Conflicts of interest
There are no conflicts of interest.

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