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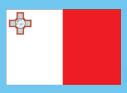

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TOPIC HIGHLIGHT

Didier Vieau, Professor, *Series Editor*

Is perinatal neuroendocrine programming involved in the developmental origins of metabolic disorders?

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Abstract

The discovery that small size at birth and during infancy are associated with a higher risk of diabetes and related metabolic disease in later life has pointed to the importance of developmental factors in these conditions. The birth size associations are thought to reflect exposure to adverse environmental factors during early development but the mechanisms involved are still not fully understood. Animal and human work has pointed to the importance of changes in the set-point of a number of key hormonal systems controlling growth and development. These include the IGF-1/GH axis, gonadal hormones and, in particular, the systems mediating the classical stress response. Several studies show that small size at birth is linked with increased activity of the hypothalamic-pituitary-adrenal axis and sympathoadrenal system in adult life. More recent human studies have shown associations between specific adverse experiences during pregnancy, such as famine or the consumption of adverse diets, and enhanced stress responses many decades later. The mediators of these neuroendocrine responses are biologically potent and are likely to have a direct influence on the risk of metabolic disease. These neuroendocrine changes may also have an evolutionary basis being part of broader process, termed phenotypic plasticity, by which adverse environmental cues experienced during development modify the structure and physiology of the adult towards a phenotype adapted for adversity. The changes are clearly advantageous if they lead to a phenotype which is well-adapted for the adult environment, but may lead to disease if there is subsequent overnutrition or other unexpected environmental conditions.

Key words: Neuroendocrine fetal programming; Metabolic disease; Diabetes; Hypothalamic-pituitary-adrenal axis; Stress responses; Birth weight

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INTRODUCTION

Evidence that adult type 2 diabetes and related metabolic conditions might have a developmental origin came originally from a series of studies showing that they were associated with small size at birth[1,2]. Size at birth is the product of a fetus' trajectory of growth, which is set up at an early stage in development, and the maternoplacental capacity to supply sufficient nutrients and oxygen to

maintain that trajectory. Although many factors contribute towards fetal growth, reductions in fetal size at term in otherwise normal population are thought to reflect fetal environmental adversity. However, it is clearly a surrogate marker that itself is probably not causally linked with long-term risks of diabetes and metabolic disease. It is generally recognised that measurements such as birth and infant weights are crude measurements that only represent a summary measure of the success of fetal and infant development. However, recent studies demonstrate associations between specific maternal adversities, such as undernutrition during pregnancy, and features of the metabolic syndrome[3].

One important feature of the epidemiological findings is that the associations with metabolic disease are graded across the birth weight range. Not all small babies develop diabetes and the proportion affected generally declines with increasing birth weight. In addition, birth weight or other measures of fetal growth are not linear measurements of developmental potential. Fetal overgrowth or macrosomia is often linked with maternal diabetes and is known to predispose to obesity, metabolic and vascular disease in later life. Consequently, many studies report inverse J-shaped or U-shaped relationships between measures of early growth and subsequent disease risk. So, for example, diabetes is associated with both low and high birth weights. However, despite the shortcomings of these measurements, a body of evidence has emerged linking patterns of fetal growth with metabolic outcomes in later life[2].

Despite the substantial evidence that an adverse early environment as indicated by small size at birth is linked with a higher prevalence of metabolic disease in adult life, it is still unclear as to how events *in utero* can affect disease predisposition some five to six decades later. Recently there has been much interest in the possibility that the early environment may have long-term effects through resetting a diverse array of hormonal systems that control growth and development. It has been known for a long time that the set point of these systems is plastic and can be programmed or permanently altered by events *in utero* or early infancy[4]. Several neuroendocrine systems appear to be involved but of particular importance is evidence that the major hormonal systems which mediate the stress response including the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system are involved[4]. Because the hormonal mediators of the stress response, including glucocorticoids and catecholamines, have biologically potent effects on metabolism and the vasculature, it has proved to be an attractive idea that these may have an important role in mediating the effects of the early environment.

PERINATAL PROGRAMMING OF THE NEUROENDOCRINE STRESS RESPONSE

Animal studies

A very large number of animal studies have clearly demonstrated that manipulation of the fetal or early post-natal environment can profoundly influence stress responsiveness and behaviors in later life in juvenile and adult offspring[5-7]. As a general consensus, maternal stress during pregnancy leads to increased HPA activity in rat, guinea pig and primate offspring. However, the outcomes of these animal studies have been quite variable. Within a species, outcomes in the offspring have been shown to be highly dependent on the nature of the maternal manipulation (i.e., maternal stress, glucocorticoid exposure, undernutrition or overnutrition) as well as the timing, intensity and duration of the manipulation in pregnancy. For example, while maternal stress in the guinea pig in late gestation leads to elevated HPA activity in male offspring, exposure to synthetic glucocorticoid, at very similar times in gestation, results in adult offspring that exhibit reduced HPA activity[8,9]. Timing of exposure is also critical. A brief exposure to maternal stress at 70% of the duration of gestation in the guinea pig resulted in adult male offspring that exhibited elevated baseline plasma cortisol levels but normal adrenocortical responses to stress. In contrast, an identical stress given at 90% of the duration of gestation resulted in adult male offspring that exhibited normal basal cortisol concentrations but increased cortisol responses to challenge[8]. Outcomes in offspring following maternal manipulation are also dependent on sex, age at which the outcome analysis is undertaken and, in females, the stage of the reproductive cycle when outcome is assessed. As an example, adult female guinea pigs, born to mothers exposed to stress in late gestation, showed a reduced cortisol response to stress compared to control offspring, but only in the estrous phase of the reproductive cycle[10]. Overall, females are underrepresented in studies undertaken in animal models, likely due to the considerations above. There also appears to be strong interaction between the prenatal and post-natal environments, such that manipulation of the post-natal environment (such as cross-fostering) can reduce or reverse the effects of the prenatal manipulation.

Modification of the early post-natal environment can also have profound influences on HPA function and behaviors. A large number of these studies have been undertaken in mice and rats. Manipulations have included altered levels of maternal care, neonatal handling of pups and maternal stress during lactation[11-13]. In this regard, neonatal handling and increased levels of maternal care lead to a reduction in basal HPA function and a reduced response to stress in adult offspring. In contrast, maternal stress during the postnatal period leads to increased HPA function and increased depressive-like behaviors in adult mouse offspring[12,14]. In summary, it is clear that the developing HPA axis is very vulnerable to the effects of early environment, which result in lifelong changes in adrenocortical function.

Many of the differences that have been observed between species likely arise from differences in the profile of fetal body and brain development that exist between species. Neuroendocrine development appears to be most

vulnerable during phases of rapid brain growth[15]. Rapid brain growth occurs during fetal life in sheep, guinea pigs and many primates. In humans, the rapid phase of brain development is initiated in the last trimester and extends into the neonatal period. However, in many rodent species, including rats and mice, maximal brain growth is not initiated until approximately 7 d after birth. As such, a period of maternal stress in the guinea pig at mid-gestation would correspond to a very different phase of fetal brain and neuroendocrine development in the mouse or rat at the same stage of gestation.

Most recently it has been shown that prenatal stress, maternal glucocorticoid treatment, maternal nutrient restriction and maternal stress during lactation can have transgenerational influences on HPA function, metabolic and cardiovascular function, and behaviors[12,16,17]. Considerable work is now being undertaken to determine the mechanisms involved in this process. Emerging evidence suggests that these include epigenetic modifications that can be transmitted through the germline[12,18].

Human studies

There have now been a number of studies which have reported associations between birth size and fasting plasma cortisol concentrations. In the Hertfordshire Cohort Study, a birth to death study of a large number of men and women born in the country of Hertfordshire, England, between 1920 and 1930, fasting cortisol concentrations decreased linearly from 408 nmol/L in those who weighed 5.5 lb or less to 309 nmol/L amongst those who weighed 9.5 lb or more, a trend which was paralleled by the concentration of the biologically active, free hormone concentrations[19]. Similar findings have been reported in other populations and a meta-analysis of 11 studies of the relationship between birth weight and cortisol concentrations reported that cortisol concentrations fell on average by 25.3 nmol/L/kg (95% CI: 5.9-44.8) increase in birth weight[20]. In more detailed studies in the Hertfordshire Cohort Study, lower birth weight was found to be associated with enhanced plasma cortisol responses to Synacthen ($ACTH_{1-24}$) in both men and women[21]. The cortisol response following an ACTH (adrenocorticotropic hormone) stimulation test reflects both adrenal size and the trophic effect of ACTH stimulation but does not elucidate the reason for the increased HPA activity in men or women of low birth weight. A number of groups have reported that the secretion of cortisol in the unstressed state did not appear to be related to birth weight. Hence, the previously observed relationship between birth weight and morning cortisol concentrations was not caused by alteration in the underlying rhythm of cortisol secretion but rather might represent a stress response involving higher centers in the brain and probably occurring as a result of the combination of fasting and the novel clinic setting in which the blood samples were obtained. A number of studies now suggest that people with low birth weight do have an enhanced biological response to stress. Studies of a large cohort of Swedish army recruits have shown a continuous relationship between size at birth and stress susceptibility at a psychological assessment which was carried out to assess their suitability for military combat duties[22]. These results are supported by a study of 106 young healthy males who were exposed to the Trier Social Stress Test: a psychological stress test involving a public speaking task[23]. These findings were also supported by a study of young children born in Southampton, who formed part of a prospective study of mothers and babies born at Princess Ann Hospital, Southampton. Again using the Trier test, a cross-sectional study of 68 boys and 72 girls (aged 7-9 years) was realized. In boys, markers of fetal growth restriction, such as low birth weight, were associated with raised arterial pressure and systemic vascular resistance, particularly following the stress test[24]. In contrast, girls who were small at birth showed no such associations, but did show greater cardiac sympathetic nervous system activation as indicated by measures of pre-ejection period and corrected QT interval, both at rest and during stress[25]. The findings of these studies suggested that there were marked gender differences in the nature of the relationship between size at birth and the stress response which reflect many of the findings of animal studies.

Other adverse maternal factors during pregnancy, such as famine or the consumption of unusual diets, are also associated with alterations in the biological response to stress[26,27], again supporting the idea that these neuroendocrine changes are not merely a consequence of low birth weight *per se* but rather a response to adversity.

Relatively little is known about the relationship between infant growth and the development of the stress response. However, work in two groups of Jamaican children who experienced growth retardation during infancy has shown that in comparison with controls, stunted children have higher heart rates, raised salivary cortisol concentrations and increased urinary catecholamine secretion following a psychological stressor[28].

Neuroendocrine stress response and the metabolic syndrome

A number of studies utilizing animal models have shown that the same prenatal and postnatal manipulations that lead to programming of HPA function and behaviors also lead to altered cardiovascular function and glucose homeostasis, and predisposition to metabolic disease. It is well established that the HPA axis plays a major role in the regulation of metabolic function; indeed, modification of metabolic function is a key component of the stress response[29]. As such, increases in HPA function which are known to result from these early life manipulations may lead directly to predisposition to metabolic disease. Alternatively, early life manipulation, such as maternal glucocorticoid treatment may lead to permanent changes in the development and subsequent function systems that regulate blood pressure, glucose insulin homeostasis and adipose function. For example, prenatal glucocorticoid treatment leads to permanent changes in

the expression of hepatic genes that are involved in glucose homeostasis (i.e., phosphoenolpyruvate carboxykinase[30]) and tissue specific changes in glucocorticoid receptors in the liver, brain and adipose as well as structural changes in the kidney (including reduced nephron number)[31,32].

Bjorntorp[33] was among the first to suggest that a neuroendocrine disturbance involving the HPA axis may play an important part in the causation of the metabolic syndrome in humans. As patients with Cushing's syndrome develop a severe form of the metabolic syndrome with hypertension, insulin resistance, glucose intolerance, dyslipidemia and central obesity, it is an attractive idea that less profound disturbances of the HPA might underlie the metabolic syndrome. Case-control and cross-sectional studies of people without pituitary or adrenal disease show that elevated plasma cortisol concentrations in morning samples are associated with high blood pressure, glucose intolerance, insulin resistance and hyperlipidemia[34]. However, an increasing body of evidence also suggests that physiological alterations in autonomic responses are also likely to be involved in the syndrome. For example, stress responsiveness to stressors that predominantly involve sympathetic activation are associated with carotid atherosclerosis, increased left ventricular mass and, in follow-up studies, with subsequent blood pressure and the prevalence of hypertension[35].

EVOLUTIONARY IMPLICATIONS

It is likely that these neuroendocrine mechanisms have an important evolutionary basis in that they allow adaptation of organisms to their expected postnatal environments within a single generation while genetic adaptation in response to environmental pressures would take much longer to influence survival characteristics. These short-term adaptations are part of a process known as developmental plasticity which is widely recognized in animal species, including vertebrates and invertebrates. Exposure of the mother to various forms of adversity during gestation triggers changes in the offspring phenotype affecting both morphology and physiology. These adversities include the level of resources, population density, temperature, the prevalence of parasites and the presence of predators. The phenotypic changes produced in the offspring tend to be adaptive as they are linked to an increase in offspring survival and reproductive success[36]. It is thought that the HPA axis, which is highly conserved in vertebrate taxa, plays a central role in producing these phenotypic adaptations to adversity in vertebrates. Glucocorticoids are known to influence the expression of approximately 10% of the genotype, including genes controlling metabolism, growth, repair and reproduction. Glucocorticoid exposure during growth and development leads to a variety of physiological and anatomical changes appropriate to adversity. These include insulin resistance, which reduces energy invested into growth and metabolism, the development of visceral fat to provide a fuel reserve and buffer in unpredictable conditions, and reduced skeletal muscle mass to decrease energetic demands. A heightened stress response enables greater chance of survival in a nutrient-deprived and, therefore, predator-rich environment.

It is likely that these endocrine effects are particularly important in species where the period of development and lifespan is relatively brief and the organism can respond appropriately to short-term changes in the environment. The situation is more complicated in long-lived species, including humans, where development occurs over more than one season and environmental cues operating during pregnancy may not be appropriate for the environment up to several decades later. Many of these species are "capital breeders" as the energy for reproduction is stored by the mother prior to conception[37,38]. This buffers the offspring against short-term ecological fluctuations or annual cycles but there is still need to be able to respond to longer-term changes in the environment. One suggestion as to how this could occur is for HPA axis responses in the feto-maternal unit to reflect the experiences of the prior generation or generations. Thus, the signal received by the fetus is an integrated signal conditioned not only by the mother's current environment but also by her neuroendocrine experience back to her own uterine environment, and by prior generations of the matriline. There is increasing evidence that HPA axis responses show intergenerational transmission, perhaps through epigenetic modifications[39]; this may allow the fetus to "see" an average environment sampled over several decades or even generations and make appropriate phenotypic adaptations.

CONCLUSION

Despite the wealth of animal data, neuroendocrine programming in humans is largely neglected. The mechanisms involved are clearly complex and hard to disentangle. For example, the effects of stressful influences on the mother are complex and are likely to be conditioned by other factors, such as the maternal social environment, the fetal and maternal genetic backgrounds, the maternal early environment and transgenerational effects. However, neuroendocrine programming may be a common pathway by which a wide variety of adverse external influences have long-term effects on the fetus. These influences include psychosocial stress, ergonomic challenges (for example, prolonged standing or carrying heavy loads), maternal diet (macro- and micronutrient intakes, dietary balance), the physical environment (heat or cold), exposure to environmental toxins or drugs and maternal illness. It is likely that maternal stressors affect the fetus by the transplacental passage of maternal hormones, such as cortisol. The human fetal HPA axis is well developed and functional in late gestation and able to respond to external factors, especially hypoxia and nutrient restriction. Therefore, external factors that reduce uterine blood flow would restrict fetal nutrient or oxygen supply and

may initiate a fetal stress response. Examples of these are likely to be ergonomic factors, such as prolonged standing or carrying heavy loads, or the release of maternal stress hormones that in turn reduce uterine vascular perfusion. In the human context, maternal stress may also affect the fetus by influencing maternal behaviors. These include maternal self-medication, smoking and consumption of alcohol. The effects of stressors in the neonatal period and infancy and the extent to which the neonate or infant responds to stressors are poorly understood. Yet the large body of data from animal studies in a variety of species from rodent to nonhuman primates suggests that external stressors at this time have the potential for long-term, important effects. Neonatal vulnerability to stress is likely to be enhanced by factors, such as prematurity, multiple birth, mode of delivery and low birth weight. These factors would be expected to increase the susceptibility to identifiable stressors, such as cold, trauma and surgery, illness, antigenic challenge and difficulties in establishing feeding (breast or artificial). It is important that these early influences are understood; to achieve this represents a challenge to both basic and clinical research.

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BRIEF ARTICLE

Are proton pump inhibitors a new antidiabetic drug? A cross sectional study

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Abstract

AIM: To investigate the effect of proton pump inhibitors (PPIs) on glycemic control (HbA1c) in type 2 diabetic patients.

METHODS: A cross-sectional study of consecutive inpatients admitted to hospital in any department during the first semester of the year 2010 who had a recent HbA1c measurement. The study excluded those with a diagnosis of hyperglycemic decompensation, diabetic onset or pregnancy. It compared HbA1c levels of those taking PPIs and those not.

RESULTS: A total of 97 patients were recruited. The average HbA1C level was 7.0% ± 1.2%. Overall PPI consumption was 55.7%. HbA1c was significantly lower in individuals who took PPIs: -0.6%, 95% CI: -0.12 to -0.83. People who used PPIs with some type of insulin therapy had a HbA1c reduction by -0.8%, 95% CI: -0.12 to -1.48. For the rest of subgroup analysis based on the antidiabetic drug used, PPI consumption always exhibited lower HbA1c levels.

CONCLUSION: PPIs seems to be consistently associated with better glycemic control in type 2 diabetes. HbA1c reduction observed is similar to incretin-based therapies.

Key words: Proton pump inhibitors; Diabetes mellitus; Drug therapy; Hypoglycemic agents; Incretins

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INTRODUCTION

Proton pump inhibitors (PPIs) have become one of the most commonly prescribed class of drugs whose overall safety profile is unquestionable[1].

PPIs are mainly used to treat symptoms of gastro-esophageal reflux disease and gastritis, but also to treat peptic ulcers (duodenal and gastric), drug-induced ulcers and to promote healing of erosive esophagitis[2].

They decrease secretion of gastric acid by blocking

the last enzyme in the system that actively transports acid from gastric parietal cells into the gastrointestinal lumen, hydrogen-potassium adenosine triphosphatase, also known as the proton pump[2].

A physiological effect of acid suppression with PPIs is a mild/modest hypergastrinemia which occurs with all PPIs[1]. Gastrin is known to be the major endocrine regulator of the secretory response to a protein meal, while somatostatin (SST) is a potent inhibitor of gastrin and histamine synthesis and release and therefore, of gastric acid secretion[3].

In rodents, gastrin induces islet β-cell neogenesis[4,5] and in *in vitro* studies, this hormone increases the β-cells mass[6].

A few retrospective studies in adults with diabetes appear to have shown that PPIs are associated with better glycemic control. Mefford *et al*[7] compared HbA1c levels from type 2 diabetic patients taking PPIs (7.0%) and type 2 diabetics not taking them (7.6%), obtaining significant differences.

Boj-Carceller *et al*[8], in a personal communication, in a smaller study with diabetic in-patients with poor glycemic control (33.8% were type 1 diabetic patients), found that those who were using PPIs had lower HbA1c levels (average HbA1c of 9.5%) than patients not taking PPIs (average HbA1c of 8.8%). After this, Hove *et al*[9] conducted a case-control study to investigate whether treatment with esomeprazole (a type of PPI) improved HbA1c levels in a group of type 2 diabetic patients. They found a borderline significant reduction of HbA1c by 0.7%.

There are no more studies in the literature, so it would be cost-effective to conduct one in order to evaluate if PPIs are associated with better glycemic control in type 2 diabetic patients.

MATERIALS AND METHODS

This study was a cross-sectional study. From the electronic medical record database, the authors selected consecutive patients with type 2 diabetes who had been admitted to hospital in any department during the first semester of the year 2010 and had a HbA1c measurement during their hospital stay. The study excluded those with a diagnosis of hyperglycemic decompensation, diabetic onset or pregnancy.

It compared HbA1c levels of those taking PPIs and those not taking PPIs by a two-sample *t* test. It also performed the same comparison according to the antidiabetic medication used (insulin, metformin, sulfonylurea and "others" for the rest of antidiabetic drugs) by the Mann-Whitney test.

HbA1c levels were determined by a high-performance liquid cromatograph (Adams A1c HA-8160).

Data are presented as mean ± SD and as percentages for categorical data. $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using the SPSS statistical package for Windows, version 17.0 (SPSS Inc., Chicago, IL, United States).

Table 1 Effect of treatment with proton pump inhibitors on glycemic control (HbA1c) in patients with type 2 diabetes

	Total	Insulin	Metformin	Sulfonylurea	Others antidiabetic drugs
Without PPI					
HbA1C (%)	7.3	7.6	7.4	7.2	8.0
SD (%)	1.4	1.5	1.6	1.1	1.2
n	43	19	24	11	4
With PPI					
HbA1C (%)	6.7	6.8	6.7	6.7	7.2
SD (%)	1.0	0.8	1.0	0.7	1.2
n	54	28	23	10	13
Absolute difference	-0.6	-0.8	-0.7	-0.5	-0.8
P value	0.018	0.022	NS	NS	NS

PPI: Proton pump inhibitor; NS: Not significant.

RESULTS

A total of 97 subjects were included. There were 43 (44.3%) women. The average age was 72 ± 10.8 years. Overall, PPI consumption was 55.7%. Glycemic control was acceptable (HbA1c ⩽ 7%) in 54.6% and the prevalence ratio of acceptable good metabolic control was 1.81 (95% CI: 0.74-4.42), in favor of those taking PPIs.

Table 1 presents the main results. HbA1c was significantly lower in individuals who take PPIs: -0.6% (P = 0.018), 95% CI: -0.12 to -0.83. When the study subdivided these two groups based on diabetes treatment, those taking insulin and concurrent PPIs had better glycemic control; HbAc1c of -0.8% points (P = 0.022), 95% CI: -0.12 to -1.48, compared with those taking insulin but not PPIs.

For the rest of comparisons there was a lack of statistical significance but the trend for lower HbA1c was constant in all groups taking a PPI.

DISCUSSION

The present study found a significant reduction of HbA1c by 0.6% in patients with type 2 diabetes who were taking a PPI. In patients who were taking insulin with a PPI, the reduction, also statistically significant, was 0.8%.

To date, three other studies have commented on a beneficial effect of PPIs on the glycemic control in patients with diabetes. The results of the current study are similar to Mefford *et al*[7] performed in a primary care context with a bigger population sample and have the same significant overall HbA1c reduction of -0.6% associated with PPI consumption. Although Hove *et al*[9] and the group did not obtain statistically significant differences, the reduction of HbA1c of those taking PPIs was identical 0.7%. The observation of these figures could provide interesting insights into the potential mode of action of PPIs since it is inside the range that Dipeptidyl peptidase-4 (Dpp-4) inhibitors and glucagon-like peptide-1 agonists (exenatide) appear to lower A1c levels -0.5% to -1%[10,11]. Actually, gastrin is a cousin of incretin

hormones since they are both gastrointestinal peptides, so PPIs could lower glycemia by a mechanism similar to incretin-based therapies. In fact, it is known that PPIs slow gastric emptying[12,13] which could decrease postprandrial hyperglycemic excursions, as glucagon-like peptide 1 does.

Other underlying mechanisms could be considered. Acid secretion from parietal cells in the stomach is highly regulated by a complex network of paracrine and endocrine effects. For instance, the effect of PPIs on glycemia could be explained by SST decrease. Several studies seem to show that administration of omeprazol decreased the antral SST content significantly[14,15]. SST is an inhibitory hormone that regulates numerous biological processes. SST inhibits the secretion of glucagon and insulin. Although the relationship between SST and diabetes is not clear, the rare somatostatinoma[16] and SST analogs are followed frequently by a glucose metabolism imbalance[17]. There are no studies that assess SST plasmatic concentration before and after PPI use.

In summary, PPIs may share most of the glucoregulatory effects of incretin-based therapies: increase islet-cell mass, slow gastric emptying, decrease glucagon levels, no weight gain and even adverse events such as concerns about immune function.

The authors recognize that the study has several limitations. Patient specific data were limited to that recorded in the database. Incomplete data collection about medication is possible (including doses). PPIs are commonly used among the population and sometimes not declared during anamnesis so the effect found may be underestimated.

In our hospital, the determination of gastrin is not available; this is the main reason it was not measured. Nevertheless, it is known that it is higher in patients taking PPIs.

Lastly, the analysis probably lacked power to compare HbA1c between specific diabetes treatment groups.

Close observation of the data imply that patients retrieved for this study had good glycemic control (in terms of target HbA1c). Previously the group has found also a positive effect on HbA1c in diabetic in-patients with poor glycemic control. This may be an independent effect of the severity of disease.

Despite the inherent limitations of the study design, PPIs appears to be strongly and consistently associated with better glycemic control in type 2 diabetes in the four published studies on the subject to date. The pharmacology of these drugs implies several gastrointestinal peptides, gastrin mainly, so it is not strange that the HbA1c reduction observed is similar to DPP-4 inhibitors and glucagon-like peptide-1 agonists.

Randomized clinical trials are required to evaluate the efficacy of this possible new antidiabetic drug and elucidate its mechanism of action.

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COMMENTS

Background

Type 2 diabetes mellitus is a complex disease whose physiopathology includes a progressive loss of islet β-cell function. More than one medication will be necessary for the majority of patients over time. Choices of therapies are usually made according to efficacy, safety, tolerability, cost of medications, simplicity and anticipated degree of patient adherence. New treatment strategies that take into account these characteristics will be welcome. Gastrin has been said to have trophic effects on β-cell mass. Theoretically it is similar to an incretin, a hormone released in the intestine associated with oral intake. Proton pump inhibitors (PPIs) are known to increase gastrin levels so they could be associated with better glycemic control in diabetes.

Research frontiers

PPIs are widely used, safe and not very expensive medicines. In the area of type 2 diabetes therapeutics, the research hotspot is the development of new treatment targets and new therapies. Treatments targeting the incretin system have recently generated interest. PPIs enhance gastrin, a gastrointestinal peptide close to glucagon-like peptide 1, so it would be appropriate to explore the antidiabetic properties of these drugs.

Innovations and breakthroughs

This study supports the hypothesis that PPIs are associated with better glycemic control in type 2 diabetes patients. To date, this hypothesis has been explored by three other groups, including the authors, in different clinical contexts (primary and hospital care) with positive and similar results in terms of decrease of HbA1c. **This article also speculates about the underlying mechanisms, considering an incretin-like effect.**

Applications

If these results are demonstrated in randomized clinical trials, PPIs could be a new antidiabetic drug with a good profile: no hypoglycemia events, good tolerability and safety, and with a limited price.

Terminology

PPIs are drugs used to treat symptoms of acid-related disorders and for primary prevention of gastroduodenal toxicity mainly. They include five agents: omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole.

Peer review

An interesting study in terms of the secondary effects of PPIs on glycemic control.

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Events Calendar 2011

January 14-15, 2011
AGA Clinical Congress of Gastroenterology and Hepatology: Best Practices in 2011 Miami FL, United States

January 28, 2011
Diabetes UK and External Conferences
Diabetes Awareness Training
London, United Kingdom

January 28-29, 2011
9. Gastro Forum München
Munich, Germany

February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 16-19, 2011
The 4th International Conference on Advance Technologies & Treatments for Diabetes
London, United Kingdom

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week,
Westin Bayshore, Vancouver
British Columbia, Canada

February 28-March 1, 2011
Childhood & Adolescent Obesity: A Whole-system Strategic Approach
Abu Dhabi, United Arab Emirates

March 3-5, 2011
42nd Annual Topics in Internal Medicine
Gainesville, FL, United States

March 14-17, 2011
British Society of Gastroenterology Annual Meeting 2011, Birmingham
England, United Kingdom

March 17-20, 2011
Mayo Clinic Gastroenterology & Hepatology
Jacksonville, FL , United States

March 18, 2011
UC Davis Health Informatics: Change Management and Health Informatics, The Keys to Health Reform
Sacramento, CA, United States

March 25-27, 2011
MedicReS IC 2011 Good Medical Research
Istanbul, Turkey
March 28–30, 2011
The Second World Congress on Interventional Therapies for Type 2 Diabetes
New York, United States

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

May 7-10, 2011
Digestive Disease Week
Chicago, IL, United States

June 2-5, 2011
The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

August 3-6, 2011
AADE 38th Annual Meeting
Las Vegas, United States
October 16-18, 2011
ISPAD Science School for Health Professionals
Miami, Unites States

October 19-22, 2011
ISPAD 36th Annual Meeting
Miami, United States

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 26-29, 2011
CDA/CSEM Professional Conference and Annual Meetings
Toronto, Ontario, Canada

October 28-November 2, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC, United States

November 10-12, 2011
The Second International Diabetes & Obesity Forum
Istanbul, Turkey

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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

World Journal of Diabetes (*World J Diabetes*, *WJD*, online ISSN 1948-9358, DOI: 10.4239), is a monthly, open-access (OA), pe er-reviewed journal supported by an editorial board of 323 experts in diabetes mellitus research from 38 countries.

The biggest advantage of the OA model is that it provides free, full-text articles in PDF and other formats for experts and the public without registration, which eliminates the obstacle that traditional journals possess and usually delays the speed of the propagation and communication of scientific research results.

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The role of academic journals is to exhibit the scientific levels of a country, a university, a center, a department, and even a scientist, and build an important bridge for communication between scientists and the public. As we all know, the significance of the publication of scientific articles lies not only in disseminating and communicating innovative scientific achievements and academic views, as well as promoting the application of scientific achievements, but also in formally recognizing the "priority" and "copyright" of innovative achievements published, as well as evaluating research performance and academic levels. So, to realize these desired attributes of *WJD* and create a well-recognized journal, the following four types of personal benefits should be maximized. The maximization of personal benefits refers to the pursuit of the maximum personal benefits in a well-considered optimal manner without violation of the laws, ethical rules and the benefits of others. (1) Maximization of the benefits of editorial board members: The primary task of editorial board members is to give a peer review of an unpublished scientific article via online office system to evaluate its innovativeness, scientific and practical values and determine whether it should be published or not. During peer review, editorial board members can also obtain cutting-edge information in that field at first hand. As leaders in their field, they have priority to be invited to write articles and publish commentary articles. We will put peer reviewers' names and affiliations along with the article they reviewed in the journal to acknowledge their contribution; (2) Maximization of the benefits of authors: Since *WJD* is an open-access journal, readers around the world can immediately download and read, free of charge, high-quality, peer-reviewed articles from *WJD* official website, thereby realizing the goals and significance of the communication between authors and peers as well as public reading; (3) Maximization of the benefits of readers: Readers can read or use, free of charge, high-quality peer-reviewed articles without any limits, and cite the arguments, viewpoints, concepts, theories, methods, results, conclusion or facts and data of pertinent literature so as to validate the innovativeness, scientific and practical values of their own research achievements, thus ensuring that their articles have novel arguments or viewpoints, solid evidence and correct conclusion; and (4) Maximization of the benefits of employees: It is an iron law that a first-class journal is unable to exist without first-class editors, and only first-class editors can create a first-class academic journal. We insist on strengthening our team cultivation and construction so that every employee, in an open, fair and transparent environment, could contribute their wisdom to edit and publish high-quality articles, thereby realizing the maximization of the personal benefits of editorial board members, authors and readers, and yielding the greatest social and economic benefits.

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The major task of *WJD* is to report rapidly the most recent results in basic and clinical research on diabetes including: metabolic syndrome, functions of α, β, δ and PP cells of the pancreatic islets, effect of insulin and insulin resistance, pancreatic islet transplantation, adipose cells and obesity, clinical trials, clinical diagnosis and treatment, rehabilitation, nursing and prevention. This covers epidemiology, etiology, immunology, pathology, genetics, genomics, proteomics, pharmacology, pharmacokinetics, pharmacogenetics, diagnosis and therapeutics. Reports on new techniques for treating diabetes are also welcome.

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The columns in the issues of *WJD* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Article: To report innovative and original findings in diabetes; (9) Brief Article: To briefly report the novel and innovative findings in diabetes research; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJD*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of diabetes mellitus; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on basic research and clinical practice in diabetes mellitus.

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Title: Title should be less than 12 words.

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There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

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Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Data that are not statistically significant should not be noted. $^{a}P < 0.05$, $^{b}P < 0.01$ should be noted ($P > 0.05$ should not be noted). If there are other series of *P* values, $^{c}P < 0.05$ and $^{d}P < 0.01$ are used. A third series of *P* values can be expressed as $^{e}P < 0.05$ and $^{f}P < 0.01$. Other notes in tables or under illustrations should be expressed as ^{1}F, ^{2}F, ^{3}F; or sometimes as other symbols with a superscript (Arabic numerals) in the upper left corner. In a multi-curve illustration, each curve should be labeled with ●, ○, ■, □, ▲, △, *etc.*, in a certain sequence.

Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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Format

Journals

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1 **Jung EM**, Clevert DA, Schreyer AG, Schmitt S, Rennert J, Kubale R, Feuerbach S, Jung F. Evaluation of quantitative contrast harmonic imaging to assess malignancy of liver tumors: A prospective controlled two-center study. *World J Gastroenterol* 2007; **13**: 6356-6364 [PMID: 18081224 DOI: 10.3748/wjg.13.6356]

Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
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