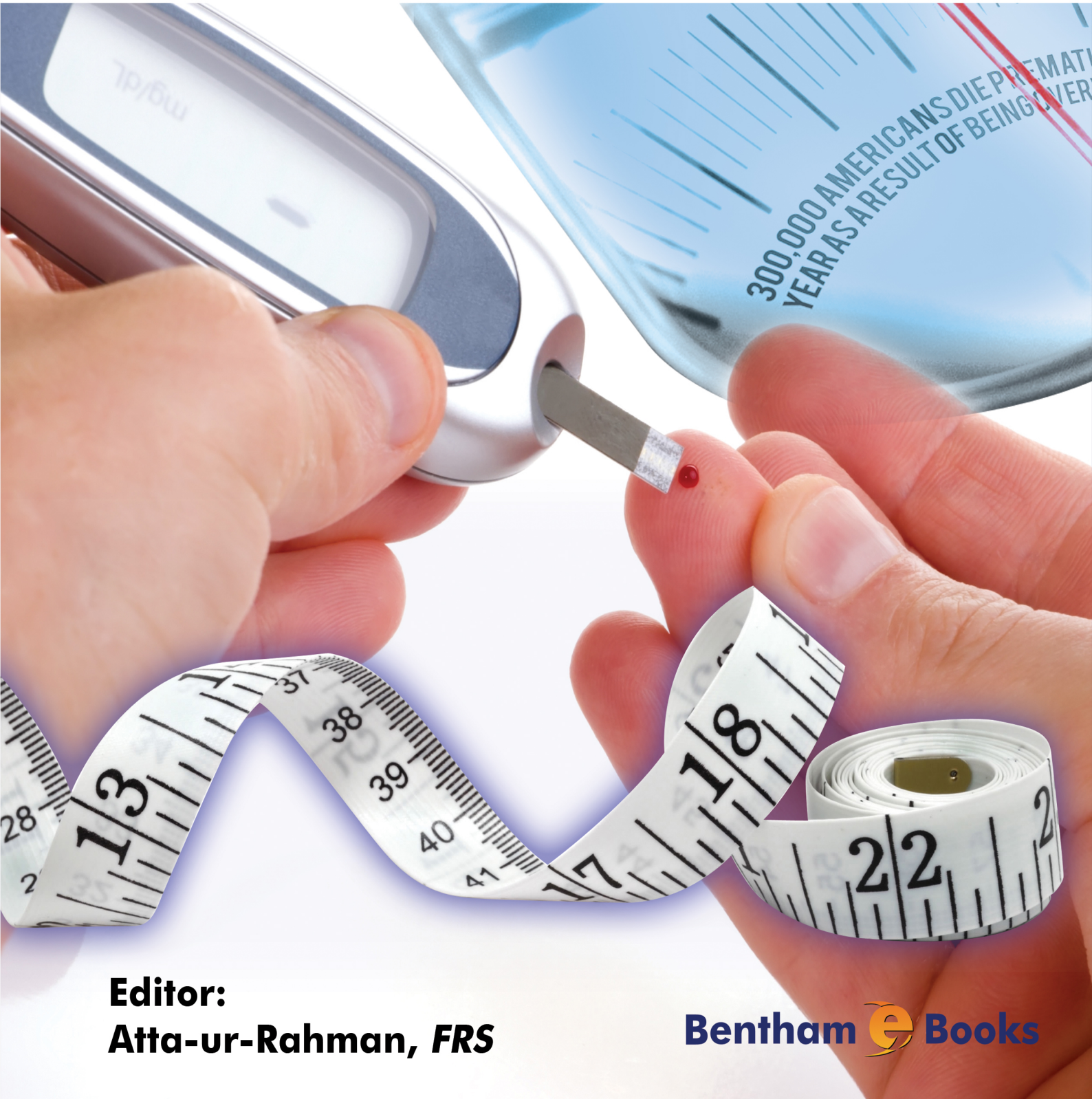
eISBN: 978-1-68108-247-9
ISBN: 978-1-68108-248-6

eISSN: 2352-3220
ISSN: 2467-9607

Frontiers in Clinical Drug Research

Volume 3

(Diabetes and Obesity)



Editor:
Atta-ur-Rahman, *FRS*

Bentham Books

Frontiers in Clinical Drug Research – Diabetes and Obesity

(Volume 3)

Editor

Atta-ur-Rahman, *FRS*
Kings College
University of Cambridge
Cambridge
UK

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eISSN (Online): 2352-3220

ISSN (Print): 2467-9607

eISBN (Online): 978-1-68108-247-9

ISBN (Print): 978-1-68108-248-6

First published in 2016.

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CONTENTS

PREFACE

Frontiers in Clinical Drug Research – Diabetes and Obesity Volume 3 comprises five comprehensive chapters on novel approaches to combat diabetes and obesity. In Chapter 1, Zhang *et al.* review the research on Extendin-4, a short peptide derived from lizard saliva, which has been used to treat diabetes and obesity. Insulin-like growth factor and growth hormone are two biochemical agents that play a role in diabetes and obesity. In Chapter 2, Moira S. Lewitt reviews the role of these two hormones in the management of diabetes and obesity.

Patients with long term diabetes suffer from heart problems and other organs are also affected. These problems have been attributed to physiological conditions brought about by the long term effects of insulin resistance on the body which result in hyperglycemic conditions and the presence of reactive oxygen species in mitochondria. In Chapter 3, Niels Juel Christensen presents a comprehensive review on insulin's effects on capillary permeability in muscle endothelial cells and in podocytes in the kidney.

In Chapter 4, Oliveira *et al.* present an interesting review on diabetes induced male infertility and pharmaceutical research being conducted to address it. The authors cover the physiology of male infertility, the epigenetics of diabetes induced changes to male gametes and the potential drug targets for treating this condition.

In Chapter 5, Katarzyna Zorena discusses the role of adipocytokines in type 2 diabetes mellitus. The author points out that monitoring concentrations of adipocytokines in the blood can be beneficial for detecting insulin resistance which leads to diabetes. Understanding adipocytokines biochemistry could be the key to prevent the early onset of type 2 diabetes mellitus.

I am very thankful to all the authors for their outstanding contributions. I would also like to appreciate the efforts of the dedicated team of Bentham Science Publishers, especially Dr. Faryal Sami (Assistant Manager Publications), Mr. Shehzad Naqvi (Senior Manager Publications) and Mr. Mahmood Alam (Director Publications).

Prof. Atta-ur-Rahman, FRS
Honorary Life Fellow
Kings College
University of Cambridge
Cambridge
UK

List of Contributors

Branca M. Silva	Health Sciences Research Centre (CICS–UBI), University of Beira Interior, Rua Marquês d'Ávila e Bolama 6200-001 Covilhã, Portugal
Katarzyna Zorena	Department of Immunobiology and Environment Microbiology, Medical University of Gdańsk, Gdańsk, Dębinki 7, Poland
Lili Cui	Pharmaceutical Biophysics Group, Institute of Pharmaceutical Science, King's College London, 150 Stamford Street, London SE1 9NH, United Kingdom
Luís Rato	Health Sciences Research Centre (CICS–UBI), University of Beira Interior, Rua Marquês d'Ávila e Bolama 6200-001 Covilhã, Portugal
Marco G. Alves	Health Sciences Research Centre (CICS–UBI), University of Beira Interior, Rua Marquês d'Ávila e Bolama 6200-001 Covilhã, Portugal
Moira S. Lewitt	School of Health Nursing and Midwifery, University of the West of Scotland, Paisley PA1 2BE, Scotland, UK
Niels J. Christensen	Herlev University Hospital, Denmark
Pedro F. Oliveira	Department of Microscopy, Laboratory of Cell Biology, Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal Unit for Multidisciplinary Research in Biomedicine (UMIB), Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal i3S - Instituto de Inovação e Investigação em Saúde, University of Porto, Porto, Portugal
Wei Kong	National Engineering Laboratory for AIDS Vaccine, School of Life Sciences, Jilin University, Changchun 130012, China Key Laboratory for Molecular Enzymology and Engineering, the Ministry of Education, School of Life Sciences, Jilin University, Changchun 130012, China
Yan Chen	National Engineering Laboratory for AIDS Vaccine, School of Life Sciences, Jilin University, Changchun 130012, China Key Laboratory for Molecular Enzymology and Engineering, the Ministry of Education, School of Life Sciences, Jilin University, Changchun 130012, China
Yong Zhang	National Engineering Laboratory for AIDS Vaccine, School of Life Sciences, Jilin University, Changchun 130012, China Key Laboratory for Molecular Enzymology and Engineering, the Ministry of Education, School of Life Sciences, Jilin University, Changchun 130012, China

CHAPTER 1

Exendin-4 and Its Derivatives for Diabetes and Obesity: Old Story and New Hope

Yong Zhang[a,b,*], **Lili Cui**[c], **Yan Chen**[a,b] and **Wei Kong**[a,b]

[a] *National Engineering Laboratory for AIDS Vaccine, School of Life Sciences, Jilin University, Changchun 130012, China*

[b] *Key Laboratory for Molecular Enzymology and Engineering, the Ministry of Education, School of Life Sciences, Jilin University, Changchun 130012, China*

[c] *Pharmaceutical Biophysics Group, Institute of Pharmaceutical Science, King's College London, 150 Stamford Street, London SE1 9NH, United Kingdom*

Abstract: Exendin-4, a 39-amino-acid peptide found in lizard saliva, is a glucagon-like peptide-1 (GLP-1) receptor agonist that has been approved for the treatment of type 2 diabetes by the United States Food and Drug Administration (FDA) since 2005. More recently, exendin-4–loaded extended-release microspheres, the first once-weekly treatment for type 2 diabetes, were also approved by the FDA in 2012. Exendin-4 exerts many beneficial anti-diabetes bioactivities, including induction of glucose-dependent insulin secretion, suppression of high glucagon secretion, slowing of gastric emptying to modulate nutrient absorption, reduction of food intake and body weight, improvement in pancreatic endocrine function, and an increase in β-cell mass. In this chapter, the historical perspective, present status and related mechanisms of exendin-4 for the treatment of type 2 diabetes are discussed. Moreover, strategies that have been applied for the design of exendin-4 derivatives and their potential applications are summarized and discussed. This chapter will benefit future prospects of the use of exendin-4 and its derivatives in the treatment of type 2 diabetes and obesity.

[*] **Corresponding author Yong Zhang:** National Engineering Laboratory for AIDS Vaccine, School of Life Sciences, Jilin University, Changchun 130012, China; Tel: +86-431-85167674; Fax: +86-43--85167751; E-mail: zhangyongking1@gmail.com

Atta-ur-Rahman (Ed.)

Keywords: Bile acid, Bioavailability, Blood glucose, Chitosan, Conjugation, Delivery system, Dimerization, Exendin-4, Fatty acid, Fusion protein, GLP-1 receptor, Human serum albumin, Modification, PEGylation, Vitamin.

INTRODUCTION

The Discovery of Exendin-4

Exendin-4, a 39-residue peptide, was discovered in 1992 by Dr. John Eng in the venom of the Gila monster *Heloderma suspectum* (Fig. **1**), which lives in the Gila River area of New Mexico and Arizona in the United States [1]. The discovery of exendin-4 was inspired by the findings of helospectin, helodermin, and exendin-3, which were isolated from the venom of lizards (*H. suspectum* and *H. horridum*) and belong to the glucagon super family of peptide hormones. Helospectin and helodermin are also called exendin-1 and exendin-2, respectively. Helospectin and helodermin have 85% sequence identity and display similar biological action, *i.e.*, promotion of cellular cyclic adenosine monophosphate (cAMP) and amylase release from dispersed acini of guinea pig pancreas [2, 3]. Helodermin is abundant in *H. suspectum* venom but is not present in *H. horridum* venom; in contrast, helospectin is present in the venoms of both lizards, but is more abundant in that from *H. horridum* [4, 5]. The high sequence identity and similar biological actions suggest that helospectin and helodermin evolved from the same ancestral lizard venom peptide. Inspired by these findings, Eng *et al.* proposed that an analogue to exendin-3 (isolated from *H. horridum* venom) might be present in *H. suspectum* venom. Besides, they found that exendin-1, -2, and -3 and other active peptides from the glucagon superfamily have the same histidine residue in their N-terminals. For these reasons, a search was performed using a chemical assay that detects peptides with N-terminal histidine residues in *H. suspectum* venom. Finally, exendin-4 was discovered [1]. The sequences of these four peptides and glucagon and glucagon-like peptide-1 (GLP-1) peptides (7-36) are shown in Fig. (**2**).

Fundamental Aspects of Exendin-4

The amino acid sequence of exendin-4 is identical to that of exendin-3 except for the presence of Gly2-Glu3 in place of Ser2-Asp3. This small structural difference

leads to distinct bioactivity. Exendin-3 can interact with both GLP-1 receptor and vasoactive intestinal peptide receptor and thus leads to increases in the release of cAMP and amylase from dispersed acini of guinea pig pancreas, whereas exendin-4 can only interact with GLP-1 receptor and thus only promotes the release of cAMP [1]. In addition, exendin-4, like exendin-3, can interact with GLP-1 receptors of gastric chief cells from guinea pig stomach and results in an increase in the secretion of cAMP and pepsinogen [6].

Fig. (1). Gila monster *Heloderma suspectum* living in Gila River area of New Mexico and Arizona in United States.

	1	5	10	15	20	25	30	35	39	Homology %
GLP-1	H A E G T F T S D V S S Y L E	G Q A A K E F I A W L V K G R								53
Glucagon	H S Q G T F T S D Y S K Y L D	S R R A Q D F V Q W L M N T								45
Exendin-1	H S D A T F T A E Y S K L L A	K L A L Q K Y L E S I L G S S	T S P R P P S S							26
Exendin-2	H S D A I F T E E Y S K L L A	K L A L Q K Y L A S I L G S R	T S P P P							20
Exendin-3	H S D G T F T S D L S K Q M E	E E A V R L F I E W L K N G G	P S S G A P P P S							95
Exendin-4	H G E G T F T S D L S K Q M E	E E A V R L F I E W L K N G G	P S S G A P P P S							100

Fig. (2). Sequences of exendin-1, -2, -3, and -4, glucagon, and GLP-1 (7-36) peptides.

CHAPTER 2

The Growth Hormone/Insulin-like Growth Factor System in the Management of Diabetes and Obesity

Moira S. Lewitt*

School of Health Nursing and Midwifery, University of the West of Scotland, Paisley PA1 2BE, Scotland, UK

Abstract: It is well recognised that the growth hormone (GH)/insulin-like growth factor (IGF) system is well recognised to have a role in diabetes and obesity. The IGFs (IGF-I and IGF-II) have structural similarity to proinsulin and the type 1 IGF receptors and insulin receptors are able to form heterodimers that participate in metabolic and mitogenic signalling. Obesity, diabetes and the metabolic syndrome are associated with alterations in the GH/IGF system. Perturbations in this system are also associated with predisposition to diabetes, obesity and the metabolic syndrome and also the risk of vascular and other complications.

Targeting this system holds therapeutic promise. Therefore, having introduced the relevant physiology and pathophysiology, the evidence base in to using GH and IGFs in the management of GH and IGFs therapy will be presented and the advantages and limitations of such approaches will be discussed.

Keywords: Diabetes mellitus, Growth hormone, Insulin-like growth factor-I, Insulin-like growth factor-binding protein-3, Insulin resistance, Obesity.

INTRODUCTION

The growth hormone (GH)/insulin-like growth factor (IGF) system is well recognised to have a role in diabetes mellitus, insulin resistance and obesity; and targeting this system in these disorders holds therapeutic promise.

* **Corresponding Author Moira S. Lewitt:** School of Health Nursing and Midwifery, University of the West of Scotland, Paisley PA1 2BE, Scotland, UK; Tel: +44 141 849 4133; Fax: +44 141 849 4302; E-mail: Moira.Lewitt@uws.ac.uk

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This chapter will first present an overview of the role of the IGF system as a system involved in metabolism, complementing and coordinating the effects of insulin. This is followed a perspective on the potential role of the GH/IGF system in the management of diabetes and obesity, and the potential risk. Following this, the use of components of the IGF system or targets for the IGF system will be reviewed, with an emphasis on the result of trials with IGF-I in type 1 and type 2 diabetes mellitus. A role for the IGF system in targeting vascular complications of diabetes and insulin resistance will not be included. Although it is clear that IGF-I is effective as an insulin sensitizer, we are far from a full understanding of this system and therefore its place in therapeutics.

In addition to clinical and experiment studies of the GH/IGF system in diabetes and obesity, there exist number of syndromes in which the function of this system is disrupted and which point to its central role in metabolism. Conditions of GH excess and deficiency demonstrate clearly that GH and IGF-I each have a different spectrum of actions. Individuals with acromegaly have evidence of increased tissue IGF-I activity including organomegaly and a predisposition to tumorigenesis, occurring in conjunction with insulin resistance due to the tissue action of GH. The use of IGF-I in conjunction with a GH receptor antagonist improves insulin sensitivity in these patients [1]. Individuals with GH insensitivity, on the other hand, have short stature and may also have insulin resistance due to reduced IGF-I activity in tissues [2]. Individuals with a polymorphism in the promoter of the IGF-I gene that reduces circulating IGF-I levels by 40% have insulin resistance and an increased risk of type 2 diabetes [3]. IGF-I gene deletion is associated with insulin resistance that responds to IGF-I treatment [4]. Thus conditions in which circulating IGF-I concentrations are low are associated with insulin resistance. This is important in designing potential approaches to management in a wider range of conditions.

Overview of the GH/IGF System

IGF-I and IGF-II are related ancestrally to proinsulin [5]. A single precursor is likely to have regulated protein metabolism for both nutrition and cell proliferation [6] and then, over the course 60 million years, the system has evolved into one that also accommodates vertebrates' complex requirements for

carbohydrate and fat storage. Although still sharing approximately 50% amino acid sequence similarity, the IGFs have a distinct role in growth and nutrition compared to insulin. While insulin is a primary short-term stimulator of metabolic activities and IGFs have longer-term roles in growth and differentiation, there is also crosstalk between the signalling of these hormones [7].

The distinct roles of insulin and IGFs are explained by a number of key differences. Most importantly, IGFs, and not insulin, are able to associate with a family of six high-affinity IGF-binding proteins (IGFBPs) that determine tissue and cell bioavailability of IGFs. Most IGFs in the circulation are bound in a high molecular mass complex with IGFBP-3, and a third, acid-labile protein, ALS. This ternary complex cannot gain access to the tissues; it therefore has a long circulating half-life (hours-days) and is considered to be a storage form of IGFs. In contrast, insulin, stored in secretory granules in pancreatic β-cells, responds rapidly to nutritional stimuli, circulates unbound in the circulation, and has a short half-life. The insulin receptor and type 1 IGF receptor are structurally similar, but differ in their affinities for insulin, IGF-I and IGF-II; furthermore there are differences in the tissue distribution of each receptor. There are also functional differences in post-receptor signalling pathways, with insulin receptors coupling to pathways involved in metabolism, and type 1 IGF-I receptors coupled to mitogenic processes. Insulin receptors dominate in adipose tissue and liver, and regulation of metabolism by insulin is more important at these sites. Any actions of IGFs on fat metabolism in these tissues are likely therefore to be indirect and, along with any effect on gluconeogenesis, due to reduction GH secretion and enhancement of insulin action [8, 9]. In muscle, on the other hand, insulin receptors, type 1 IGF receptors and their hybrid receptors [10, 11] are present; and insulin and IGF are both important in glucose and protein metabolism in muscle. Hybrid receptors bind IGF-I with high affinity, rather than insulin, and the abundance of hybrid receptors has been observed to increase in the skeletal muscle and adipose tissue of individuals with type 2 diabetes [12]. This provides a rationale for administering IGF-I in some of these patients. Much less is known about the role of IGF-II and its role in metabolic disease is reviewed elsewhere [13].

GH and IGF-I, together with insulin are part of a complex systems resulting in the

CHAPTER 3

Insulin, Cardiovascular Function and Long-Term Diabetic Complications

Niels Juel Christensen*

Herlev University Hospital, Denmark

Abstract: Patients with long-term diabetes develop angiopathy and neuropathy. Macroangiopathy refers to myocardial infarction, strokes and ischemic gangrene. Retinopathy and nephropathy are due to microangiopathy. The development of late diabetic complications is often assumed to be due to hyperglycemia and production of reactive oxygen species (ROS) in mitochondria. Despite regulation of blood glucose and blood pressure many patients still die of diabetic angiopathy. Intensive blood glucose control did reduce the risk for retinopathy and neuropathy, but had no significant effect on clinical renal outcomes. Blood pressure lowering in type 2 diabetic patients leads to a significant reduction in albuminuria, whereas improvement in renal failure was not significant. Newer therapies are therefore of vital importance. Diabetes is caused by insulin deficiency. Insulin treatment may induce insulin resistance and increase body weight. The appearance in plasma after injection is delayed, and patients may have relative high insulin values during the day. Insulin has a number of specific effects on the cardiovascular system and the kidney. This review focuses on insulin's effects on capillary permeability in muscle endothelial cells and in podocytes in the kidney. Insulin deficiency and resistance rather than hyperglycemia may be directly responsible for lack of capillary recruitment in muscles and abnormal function of podocytes in the glomerulus in the kidney. It is concluded, that it is unlikely that long-term complications can be eliminated without development of a more physiologic insulin delivery system or alternatively with development of drugs that temporarily can activate specific insulin signaling pathways in the cells.

Keywords: Bariatric surgery, Bilirubin, Blood flow, Calorie restriction, Capillary recruitment, Cardiovascular disease, Diabetic macroangiopathy,

* **Corresponding author Niels Juel Christensen:** Annasvej 26, 2900 Hellerup, Denmark; Tel: 004524485227; E-mail: nielsjue@post4.tele.dk

Atta-ur-Rahman (Ed.)

Diabetic microangiopathy, Gangrene, Hyperglycemia, Hypotension, Insulin, Insulin resistance, Insulin treatment, MSNA, Nephropathy, Neuropathy, NO, Obesity, Plasma volume, Prevention, Retinopathy, ROS, Sympathetic activity, TER, Tissue recruitment, Urinary albumin excretion.

INTRODUCTION

Patients who have had diabetes for many years may develop a specific diabetic vascular disease [1]. Diabetes mellitus is divided into two types. Type 1 (T1DM) is seen in the younger age groups and Type 2 (T2DM) in the elderly. The prevalence of T2DM is approximately 10 times that of T1DM. Diabetic angiopathy may be divided into microangiopathy and macroangiopathy. Microangiopathy includes retinopathy and nephropathy. Macroangiopathy includes myocardial infarctions, strokes and amputations. The later mentioned diseases are of course also seen in non-diabetic patients, but the clinical presentation may be different in diabetic patient and in non-diabetic subjects. The risk of developing cardiovascular disease is at least twice as high in T2DM patients compared to normal subjects.

There has been a decline in the frequency of complications between 1990-2010 especially of myocardial infarction, rates of amputations and stroke. The smallest decline was in end-stage renal disease [2]. Intensive therapy to achieve blood glucose values and glycosylated hemoglobin (hemoglobin A_{1c}) close to normal in T1DM patients reduced the development of diabetic retinopathy and neuropathy [3]. The development of albuminuria was also reduced [4]. Intensive treatment of blood glucose was associated with a significant increase in severe hypoglycemia and weight gain. This study is very successful, but it is also clear that many patients in the intensive treated group developed long-term diabetic complications.

Despite regulation of blood glucose and blood pressure many patients still die of diabetic angiopathy. In T2DM diabetic patients intensive glucose control did not reduce the risk for significant clinical renal outcomes [5]. Furthermore it has been shown in a very large systematic review and meta-analysis, that blood pressure lowering in type 2 diabetic patients leads to a significant reduction in mortality,

cardiovascular events, stroke and albuminuria, whereas improvement in renal failure was not significant [6]. Arterial hypertension in non-diabetic subjects does not induce the specific changes seen in the kidney in diabetic patients. Nevertheless one could expect that lowering of the arterial blood pressure would reduce progression of the renal disease, but this does not seem to be the case. It is possible that the reduction in albuminuria is a consequence of the reduction in blood pressure *per se* or alternatively a specific effect of some of the drugs used to treat hypertension. It cannot be excluded, that the duration of therapy has been too short in some studies to demonstrate a significant improvement, but a clear effect on albuminuria and cardiovascular disease was demonstrated. A decrease in albuminuria during antihypertensive treatment does not indicate that the risk of renal failure or end-stage renal disease is reduced. The development of newer therapies are therefore of vital importance [7].

The Role of Hyperglycemia

It has been difficult to prove a major role for hyperglycemia in the development of long-term diabetic complications perhaps especially in Type 2 diabetic patients. Nevertheless some studies mainly experimental studies have explained how high concentrations of glucose may damage the vascular and nervous system. In the Banting Lecture 2004 Brownlee [8] presented a unifying mechanism that connected a number of important findings. Hyperglycemia results in an increased production of increased reactive oxygen species (ROS) primarily superoxide. The hyperglycemia induced superoxide production results in activation of four damaging pathway: The polyol pathway, the hexosamine pathway, activation of PKC and production of advanced glycation end products (AGEs). Activation of PKC results in a decrease in eNOS (described later) and an increase in NF-κB, which is important for inflammatory responses. Furthermore it was shown that an increase in the flux of free fatty acids increased the production of reactive oxygen species (ROS) in arterial endothelial cells but not in microvascular endothelial cells. Several novel therapeutic approaches were also discussed in the Banting lecture.

Recent studies have shown that early progression in the glomerular basement membrane width in young diabetic subjects was associated with elevated levels of

CHAPTER 4

Pharmacological Relevance of Novel Biomarkers Associated with Diabetes-mellitus Related Infertility

Luís Rato[1], Marco G. Alves[1], Branca M. Silva[1] and **Pedro F. Oliveira[2,3,4,*]**

[1] *Health Sciences Research Centre (CICS–UBI), University of Beira Interior, Rua Marquês d'Ávila e Bolama 6200-001 Covilhã, Portugal*

[2] *Department of Microscopy, Laboratory of Cell Biology, Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal*

[3] *Unit for Multidisciplinary Research in Biomedicine (UMIB), Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Porto, Portugal*

[4] *i3S - Instituto de Inovação e Investigação em Saúde, University of Porto, Porto, Portugal*

Abstract: Metabolic diseases are major public health problems both in developed and developing countries. Factors associated with lifestyle including physical inactivity and excessive consumption of high-energy diets are the primary causes for the increasing incidence of these pathologies. In parallel, an unprecedented decrease of fertility rates is also being witnessed. Male reproductive health is very sensitive to the insults induced by alterations in the metabolic status and the number of men suffering from metabolic diseases (such as diabetes mellitus and obesity) is dramatically high, being expected to increase even further in the next decades.

Diabetes mellitus is associated with a decrease in male reproductive potential and known to promote several sexual disorders, such as erectile dysfunction or retrograde ejaculation. Still, the "hidden effects" of this pathology on testicular physiology may lead to even more serious consequences for male fertility. Diabetes mellitus induces shifts in testicular metabolism, particularly in glucose metabolism, which is vital for the normal occurrence of spermatogenesis. So the maintenance of testicular glucose metabolism homeodynamics is of particular relevance; otherwise spermatogenesis may

[*] **Corresponding author Pedro Fontes Oliveira:** Department of Microscopy, Laboratory of Cell Biology, Institute of Biomedical Sciences Abel Salazar (ICBAS), Rua de Jorge Viterbo Ferreira 228, 4050-313 Porto, Portugal; Tel/Fax: +351-220-428-000; E-mail: pfobox@gmail.com

Atta-ur-Rahman (Ed.)

be arrested. For many years this issue was overlooked, but compelling evidence shows that spermatogenesis only occurs under a tight metabolic control. Thus, this subject is becoming a hot topic and will be on the spotlight in the next years. On the other hand, metabolic alterations induce pressure in biological systems whose responses are mediated by epigenetic modifications, particularly in sperm. These modifications are stable and can be passed to the subsequent generations, enhancing the transmission of phenotypes. Hence, the metabolic mechanisms responsible for the alterations in male reproductive health and subfertility/infertility in diabetic individuals deserve special attention.

This chapter will present cutting-edge information on the effects of diabetes mellitus in the testicular physiology and metabolism. It will be also discussed how this metabolic disease contributes to stable epigenetic changes that may alter not only male gametes' function but also contribute to a potential transgenerational amplification of the current diabetes-related deleterious effects. Finally we will address the concept that testicular metabolism can be a potential pharmacologic target to counteract subfertility/infertility promoted by diabetes mellitus.

Keywords: Anti-diabetic drugs, Diabetes mellitus, Glucose metabolism, High-energy diets, Hormonal control, Male infertility, Metabolic diseases, Metabolic reprogramming, Natural products, Oxidative stress, Reactive oxygen species, Sertoli cells, Sperm parameters, Spermatogenesis, Spermatozoa, Testicular biomarkers, Testicular metabolism, Therapeutic target, Transgenerational effects.

1. INTRODUCTION

Today, the number of men suffering from metabolic disorders has reached unprecedented values and this situation leads us to face what is now being advocated as the biggest health crisis ever recorded worldwide [1]. In fact, this health problem has a particular incidence in modern societies, but in the near future it will be of major relevance also in developing countries. Lifestyle factors, such as erroneous eating behaviors, particularly the excessive intake of high-energy diets (HED) and/or nutrient unbalanced diets have contributed to the increase of metabolic diseases, namely obesity and diabetes mellitus (DM). Indeed, the combination of factors such as: (1) changes in the composition of foods, (2) increased consumption of HED, (3) consumption of foods with high levels of sugar and saturated fats and (4) lack of physical activity are the main causes for the increase of this pathology.

DM is a public health problem in developed countries and its incidence has likewise increased, particularly among men within reproductive age, contributing to the emergence of subfertility and infertility in these individuals. In the last decades a marked decline in reproductive health has been observed, which is already reflected in the fertility rates observed in developed countries, that reached the lowest values ever reported [2]. While the prevalence of infertility in a couple is one in seven, the male factor has been appointed as major contributor, being present in 50% of the cases [3]. In fact, the metabolic and hormonal dysregulation induced by these pathological conditions compromises the male reproductive function, not only through the hypothalamus-pituitary gonadal axis (HPT-axis) (also called as reproductive axis), which is sensitive to subtle metabolic disturbances, but also through direct alterations in the reproductive tissues [4 - 7].

Testicular tissue consists of a heterogeneous population of somatic and germ cells, where germ cells are dependent on the physical and nutritional support provided by Sertoli cells (SCs) and any metabolic disorder may alter this metabolic cooperation. In these last few years, the metabolism of testicular cells gained particular interest in this research field [8 - 13], especially SCs, since they present some unique features that are pivotal for the success of spermatogenesis [10]. SCs do not follow the same “metabolic pattern” observed in the majority of tissues where glucose is used to produce energy. Instead, SCs only use a minor part of the glucose that take up from the extracellular space for its own energy production, being the majority converted to lactate to be delivered to germ cells [14]. This “simple metabolic cooperation” is crucial to determine germ cells fate and although this event has been overlooked for many years, the control of SCs glycolytic metabolism is now on the spotlight of reproductive biologists. Indeed, the maintenance of spermatogenesis is highly dependent on the metabolic cooperation established between SCs and germ cells. The mechanisms that regulate the metabolism of SCs are essential for spermatogenesis and this metabolic process is regulated by a plethora of hormones and endogenous factors that constitute an intricate network of signals and orchestrate various metabolic pathways (for review see [8, 15]). Disruption of these tightly regulated pathways alters the glycolytic metabolism of SCs, compromising one of their main

CHAPTER 5

Obesity and Type 2 Diabetes Mellitus: Adipocytokines as Markers of Insulin Resistance

Katarzyna Zorena*

Department of Immunobiology and Environment Microbiology, Medical University of Gdańsk, Gdańsk, Dębinki 7, Poland

Abstract: The obesity epidemic has become one of the major challenges for the modern society, first of all because of its clinical and social consequences. In 1998 the World Health Organization (WHO) proclaimed obesity a worldwide epidemic encompassing both adults and children and acknowledged it one of the biggest threats to the human health. The cause of overweight and obesity is body mass increase as a result of fat tissue increment. It has been proven that obesity increases the risk of hypertension, type 2 diabetes (T2DM), as well as leads to cardiovascular complications such as stroke or heart attack. The fat tissue that is superfluous in obesity is the source of many hormonally active compounds influencing bodily homeostasis. The recent research has pointed to the particular importance of abdominal obesity in the pathogenesis of metabolic disturbances linked with the endocrine activity of the visceral fat. This visceral fat tissue produces many adipokines, such as tumour necrosis factor alpha (TNF-alpha), interleukin 6 (IL6), leptin, adiponectin, resistin, omentin, visfatin, nesfatin, vaspin, chemerin, ghrelin or apelin. Adipocytokines, released into the bloodstream thanks to specific receptors on the surface of the target cells, act as classic hormones influencing organ and tissue metabolism. Moreover adipokines may decrease tissue sensitivity to insulin and induce inflammatory processes, endothelial dysfunction and atherosclerotic changes. At present much attention is given to determination of adipokines as contemporary markers of insulin resistance. Research authors suggest that changes in adipokine concentrations can be seen at least a few years earlier that first symptoms of improper glucose metabolism. Although there are still many controversies regarding what is the most important causative factor for T2DM, it cannot be denied that the endocrine activity of fat tissue as well as the immunological

* **Corresponding Author Katarzyna Zorena:** Department of Immunobiology and Environment Microbiology, Medical University of Gdańsk, Gdańsk, Dębinki 7, Poland; Tel/Fax: +48583491766; Email: kzorena@gumed.edu.pl

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status both play important roles in the pathogenesis of T2DM. Promising research results point to the necessity of elaborating methods of measuring pro-inflammatory factors, especially adipokines, that would be both diagnostically sensitive and specific and that could be implemented in the laboratory diagnostics as well as primary prevention of diabetes.

Keywords: Obesity, Insulin resistance, Lipid metabolism disorders, Arterial hypertension, Type 2 diabetes mellitus, Leptin, Adiponectin, Resistin, Retinol binding protein 4, Visfatin, Omentin, Vaspin, Chemerin, Apelin.

1. OBESITY AND EPIDEMIOLOGY OF OBESITY

As estimated by the World Health Organization (WHO), currently all over the world there are 1.6 billion overweight and more than 522 million obese people. The WHO has recognised obesity as the most common metabolic disease and a pandemic of the 21st century. Excess body weight is the fifth most common risk factor for death worldwide. Each year almost 2.8 million adults all over the world die from consequences of overweight and obesity and in spite of this the prevalence of obesity continues to be high and is still increasing [1]. The increasing prevalence of overweight and obesity is a problem not only in developed countries but also in developing nations. In the developing countries overweight and obesity coexist with undernutrition. The prevalence of obesity among adults in the Eastern Europe, Eastern Mediterranean, Spain and Italy is equally high as in the United States of America. According to the *Centers for Disease Control and Prevention (CDC),* in years 2009–2010 more than one third of the USA population (35.7%) was obese [1, 2]. In Europe obesity affects 4.0–28.3% of males and 6.2–35.6% of females. The highest obesity rates are observed in the Central, Eastern and Southern Europe whereas the lowest obesity rate is found in the Southeastern Europe [3]. The World Health Organization estimates that the number of obese people worldwide doubled from 1980 to 2000. In 2008 35% of adults of 20 or more years old were overweight and 11% were obese. According to the latest WHO data, more than 65% of global population live in countries where the risk of death is higher from overweight and obesity than from underweight [1, 4]. According to the self-reported data presented in the Organisation for Economic Co-operation and Development (OECD) Report from

2012, 53% of adult population living in the OECD member states have excess body weight, obesity or overweight [5 - 7].

The prevalence of obesity in the OECD member states varies from low in South Korea or Japan, where obese people make 4% of population, too high in the United States and Mexico, where the corresponding ratio is 30% (*Source:* IDF (2009), OECD Health at a Glance 2011). 18% of adult population in the OECD countries are obese. Although the proportions of obese men and women are in general similar, some disparities may occur. In Chile, Turkey and Mexico the proportion of women is higher while in Island and Norway it is men that make a higher proportion of obese. Currently available data show that increasing prevalence of obesity is seen in all socioeconomic groups regardless of age, sex, race, income and education level [5].

According to the European Nutrition and Health Report, the highest percentage of obese people in Europe is made by inhabitants of Greece, with 28% of men and 38% of women being obese. The lowest rates of obesity are seen in France, Sweden, Denmark and Norway, where obesity affects 7-9% of men and 6-8% of women [7]. In China, Japan and most African countries obesity is still a relatively uncommon problem. However the situation in these countries is changing to the worse from year to year along with changing nutrition habits and growing popularity of fast food [8 - 10]. The widespread availability of highly processed foods, which is easy to serve and does need any processing, is one of the factors that contribute to the growing prevalence of obesity all over the world. Obesity is not only a major health problem, with increasing incidence of hypertension, coronary artery disease, type 2 diabetes and premature deaths, but also an economic burden. Costs of obesity-related medical treatments make about 5% of the total health care expenditures in the United Kingdom and 2-7% all over Europe [11 - 13].

1.1. Diagnostic Tools that Help Diagnose Obesity

Obesity is an abnormal accumulation of body fat, usually 20% or more over an individual's ideal body weight. Obesity is diagnosed when the percentage of body fat is higher than 25% in men and 30% in women [14]. Obesity is also recognized

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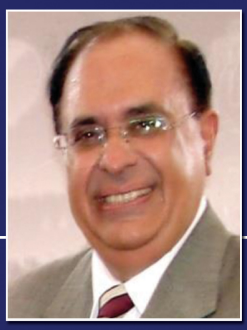

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Atta-ur-Rahman, Ph.D. in organic chemistry from Cambridge University (1968), has 1020 international publications in several fields of organic chemistry including 727 research publications, 37 international patents, 68 chapters in books and 188 books published largely by major U.S. and European presses. He is the Editor-in-Chief of eight European Chemistry journals. He is Editor of the world's leading encyclopedic series of volumes on natural products "Studies in Natural Product Chemistry" 50 volumes of which have been published under his Editorship by Elsevier during the last two decades.

Prof. Rahman won the UNESCO Science Prize (1999) and was elected as Fellow of the prestigious Royal Society (London) in July 2006. He has been conferred honorary doctorate degrees by many universities including (Sc.D.) by the Cambridge University (UK) (1987). He was elected Honorary Life Fellow of Kings College, Cambridge University, UK, conferred the TWAS (Italy) Prize and the Austrian government has honoured him with its high civil award ("Grosse Goldene Ehrenzeischen am Bande") (2007). He is Foreign Fellow of Chinese and Korean Academy of Sciences, Foreign Fellow of the Chinese Chemical Society and former President of Pakistan Academy of Sciences.