Extrapancreatic actions of incretin-based therapies on bone in diabetes mellitus

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SUMMARY

Diabetes mellitus is correlated with modifications in bone microarchitectural and mechanical strength, leading to increased bone fragility. The incretin hormones, with a classical effect to increase insulin secretion following food ingestion, are now postulated to have important direct effects on bone. As such, glucose-dependent insulinotropic polypeptide (GIP) has dual actions on bone cells; enhancing bone-forming activity of osteoblasts and suppressing bone resorption by osteoclasts. The sister incretin of GIP, glucagon-like peptide-1 (GLP-1), is also suspected to directly influence bone health in a beneficial manner, although mechanism are less clear at present. The physiological actions of incretins are attenuated by dipeptidyl peptidase (DPP-4) activity and it is speculated that introduction of DPP-4 inhibitor may also positively affect quality of the skeleton. As such, this thesis evaluates the potential beneficial effects of a DPP-4 resistant GIP analogue, namely [D-Ala^2]GIP, on osteoblastic-derived, SaOS-2 cells, and also preliminary *in vivo* studies on the impact of genetic deficiencies of GIPRs and GLP-1Rs on bone mineral density and content. Further studies characterised the beneficial effects of incretin-based therapies on metabolic control, bone microstructure and bone mechanical integrity in animal models of pharmacologically-, genetically- and environmentally-induced diabetes. GIP and related stable analogue increased bone-forming biomarkers in SaOS-2 cells and importantly, [D-Ala^2]GIP was shown to be more potent than native GIP. Knockout mouse studies revealed that both GIPR and GLP-1R signaling are important for optimum bone mass. All diabetic mouse models displayed reduced bone mass, altered bone micromorphology and impairment of bone mechanical strength, similar to the human situation, confirming their appropriateness. The incretin-based therapeutics, [D-Ala^2]GIP and Liraglutide, in streptozotocin-diabetic significantly increased bone matrix properties, indicating recovery of bone strength at the tissue level. The beneficial effects of administration of [D-Ala^2]GIP-oxyntomodulin on bone health in *db/db* mice were more prominent as the Oxm analogue did not only improve bone strength at tissue level, but also at whole-bone level. These modifications were independent of metabolic status. Twice-daily Exendin-4 therapy improved glycaemic control and increased work required to resist bone fracture in high-fat fed mice. It was also established that Sitagliptin had neutral effects on bone microstructure and mechanical strength in high-fat mice. In

summary, these data demonstrate the negative impact of diabetes mellitus on normal skeleton development and bone quality. Moreover, this thesis highlights the growing potential of incretin-based therapies for ameliorating bone defects and improving the increased fragility fracture risk associated with diabetes.

ABBREVIATIONS

AGEs	Advanced glycation end products
AlkP	Alkaline phosphatase
AMD	Absorbing mineral density
AUC	Area under the curve
B.Dm	Bone diameter
BMC	Bone mineral content
BMD	Bone mineral density
BMDD	Bone mineral density distribution
BSE	Back-scattered electron
BV	Bone volume
bw	Body weight
cAMP	Cyclic adenosine monophosphate
cm	Centimeter
CSMI	Cross-sectional moment of inertia
Ct.Th	Cortical thickness
(*db/db*)	Diabetic (*db/db*) mice
DEXA	Dual-energy x-ray absorptiometry
dl	Decilitre
DM	Diabetes mellitus
FBS	Fetal bovine serum
g	Gram
GIP	Glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
GL	Grey level
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
GPa	Gigapascal
h	Hour
ip	Intraperitoneal injection
keV	Kilo electron volt
kg	Kilogram
KO	Knock-out mice

kV	Kilovolt
l	Litre
Ma.Dm	Marrow diameter
MALDI-TOF-MS	Matrix-assisted laser desorption/ionization-time of flight mass spectrometry
mg	Miligram
microCT	X-ray microcomputed tomography
min	Minutes
ml	Mililitre
mm	Milimeter
mmol	Milimolar
MMP	Matrix metalloproteinase
mN	Milinewton
MPa	Megapascal
MSC	Mesenchymal stem cell
N	Newton
nm	Nanometer
OPG	Osteoprotegerin
Oxm	Oxyntomodulin
pA	Picoampere
pJ	Picojoule
PMMA	Polymethylmethacrylate
qBEI	Quantitative back-scattered electron imaging
qXRI	Quantitative x-ray imaging
RANKL	Receptor activator on nuclear factor-Kappa B ligand
RIA	Radioimmunoassay
ROI	Region of interest
rpm	Revolutions per minute
RT-PCR	Reverse transcriptase-polymerase chain reaction
SEM	Standard error of the mean
STZ	Streptozotocin
Tb.N	Trabecular number
Tb.Sp	Trabecular separation
Tb.Th	Trabecular thickness

TRAP	Tartrate-resistant acid phosphatase
TV	Trabecular volume
U	Unit
Z	Atomic number
µA	Microampere
µg	Microgram
µl	Microlitre
µm	Micrometer

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Chapter 1

General Introduction

1.0 OVERVIEW

Diabetes has become a global issue as it is estimated that more than 387 million people worldwide are affected by this modern disease (International Diabetes Federation 2014b). The alarming number of diabetes cases has listed this disorder as the potential seventh leading cause of death in 2030 (Mathers & Loncar 2006). Common complications that are associated with diabetes include retinopathy (blindness), neuropathy (nerve damage), cardiovascular disease, stroke and nephropathy (kidney failure) (Diabetes UK 2014) and most recently, diabetes is also related to bone loss. Extensive studies on the impact of diabetes on bone have linked the disease to severe impairment of bone mechanical integrity, reduced bone mineral density (BMD) in T1DM and unaffected or even increased BMD in T2DM. Regardless of the inconsistencies in BMD, both types of diabetic patients have increased risk of fractures (Janghorbani et al. 2007, Vestergaard 2007). Early diagnosis and treatment of diabetes is vital to prevent long term complications that could lead to bone fractures and mortality in elderly people. Furthermore, the link between diabetes and bone fragility suggests that if blood glucose management is improved or if signaling pathways contributing to diabetic bone pathologies are corrected, overall bone quality could be enhanced, improving the increased risk of fracture in diabetic patients.

1.1 DIABETES MELLITUS

Diabetes mellitus (DM) is a metabolic disease where production of insulin is insufficient or body cannot effectively utilise insulin produced by pancreas. As a consequence, there will be high blood glucose levels in the body. Diagnosis of diabetes mellitus is made when fasting plasma glucose is ≥ 126 mg/dl (7.0 mmol/l) or plasma glucose level is ≥ 200 mg/dl (11.1 mmol/l) measured 2 hours after 75 g-oral glucose tolerance test (Zemmit et al. 2001). Generally, the disease is classified into 2 major forms; type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

1.1.1 Type 1 diabetes mellitus

Type 1 diabetes mellitus (T1DM), previously referred to as juvenile-onset or insulin-dependent diabetes, is characterised by inability of the body to synthesise insulin due to destruction of insulin-producing pancreatic beta cells. This results in a dependency on exogenous insulin to stabilise blood glucose concentrations following feeding. The pathogenesis of this autoimmune disorder has been extensively studied in rodent models and humans and several key target for autoantibodies and autoreactive cells have been identified; insulin, glutamic acid decarboxylase (GAD), protein tyrosine phosphatase insulinoma antigen (IA-2), zinc transporter 8 (ZnT8) and islet glucose-6-phosphatase catalytic subunit-related protein (IGRP) (Culina et al. 2013, Yoon & Jun 2005, Zhang et al. 2008). Pancreatic beta cells autoantigens together with lymphocytes and macrophages trigger overexpression of $CD4^+$ and beta cell-specific cytotoxic $CD8^+$ T cells (Pinkse et al. 2005) which eventually lead to the destruction of insulin-producing beta cells.

The primary cause of T1DM is autoimmune beta-cell destruction. However, there is also correlation between genetic and several environmental factors in the pathogenesis of TIDM. Genetic components that strongly influence T1DM are reported to be on major histocompatibility complex human leukocyte antigen (HLA) alleles, which are associated with 'protection from' or 'susceptibility towards' T1DM. More than 90% of TIDM patients have either DR3-DQ2 or DR4-DQ8 haplotypes, while the percentage of normal controls with these haplotypes is less than 40% (Atkinson & Eisenbarth 2001). These genes are known to be important regulators in immune response by introducing peptide antigens to T lymphocytes which stimulate the production of antibodies against beta-cell antigens. Further exposure to environmental triggers such as viruses in susceptible individuals can cause abnormal activation of immune system that will generate multiple autoantibodies to islet cells.

T1DM is most prevalent in children and young people and it accounts for about 10% of diabetes cases worldwide (International Diabetes Federation 2014a). Statistical studies conducted by EURODIAB (EUROpe and DIABetes) from 1989 to 2003 estimated that diabetes cases in children below 15 years old will rise by 70% in 2020

(Patterson et al. 2009). A more recent study on trends over 20-year incidence projected that the prevalence of Type 1 diabetes has annual increase of 3.4% (Patterson et al. 2012).

1.1.2 Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM), previously known as adult-onset or non-insulin-dependent diabetes, develops when beta cells do not make enough insulin or the insulin produced does not work appropriately. T2DM is a progressive disease and starts gradually with insulin insensitivity or impairment of the body's response to insulin (Stumvoll et al. 2005). Compensatory mechanism in the body respond to insulin resistance by secreting more insulin to maintain normal glucose levels, but eventually pancreatic beta-cells can no longer produce sufficient insulin to maintain normal glucose levels. Over time, worsening insulin resistance and the decline in beta cell function will lead to hyperglycaemia and eventually progress to the diabetic state. The environmental factors that trigger T2DM are pregnancy, ageing and modern lifestyle (high calorie intake, obesity, physical inactivity) (Chen et al. 1988, Hu 2011, Stumvoll et al. 2005). Similar to T1DM, the combination of genetic predisposition and environmental factors contributes to the onset of insulin resistance and its progression to T2DM (Leahy 2005). The key genes associated with genetic predisposition of T2DM are *TCF7L2*, *PPARG*, *KCNJ11*, *CAPN10*, *HHEXIIDE*, *MC4R*, *FTO* and *KCNQ1* (Tahrani et al. 2011, Valeriya et al. 2007).

T2DM usually appears in middle-aged and older people and accounts for 90% of all diabetes cases (International Diabetes Federation 2014a). T2DM has become an epidemic as this disease progresses slowly and undetected many years before diagnosis is made. With increasing prevalence of obesity and T2DM, a huge burden is imposed on the public health-system (Diabetes UK 2012).

1.1.3 Existing treatment for diabetes

The only therapeutic option for T1DM patients is exogenous insulin replacement therapy. However, T1DM complications are not always prevented by exogenous insulin therapy (Atkinson et al. 2014). Other important glucoregulatory hormone which is co-secreted with insulin by pancreatic beta cells, amylin, is also reduced in T1DM, leading to generation of synthetic amylin analogue, Pramlintide. Amylin replacement with Pramlintide improves glycaemic control by delaying gastric emptying and suppressing postprandial glucagon secretion (Fineman et al. 2002, Nyholm et al. 1999). In a long term clinical study, adjunct therapy with Pramlintide has been shown to provide better glycaemic control in T1DM individuals compared to insulin replacement alone (Ratner et al. 2004). As such, this amylin-related analogue was clinically approved in April 2004 by the US Food and Drug Administration (FDA) to be used as add-on with insulin therapy in T1DM patients (Ryan et al. 2005). Another option for T1DM treatment is islet-cell transplantation, leaving the recipients dependent on lifelong immunosuppression drugs to prevent organ rejection. Most importantly, the limiting factor in this type of treatment is a short supply of organs and until new sources of functional islets are found, the future for organ transplantation in T1DM treatment remains sceptical (McCall & Shapiro 2012).

Obesity is normally associated with impaired glucose tolerance and increased risk of developing T2DM. This is due to increased adipocyte accumulation of non-esterified fatty acids, hormones, inflammatory cytokines and other molecules that are involved in the development of insulin resistance (Kahn et al. 2006). Essentially, insulin resistance is improved through intensive lifestyle intervention by monitoring nutritient intake and regular physical activity (Tahrani et al. 2011). However, lifestyle changes are difficult to maintain and not sufficient to keep blood glucose levels normal. Consequently, oral or injectable antidiabetic drugs are often required to manage T2DM (International Diabetes Federation 2014a). Currently available T2DM treatments are summarised in Table 1.1.

Chapter 8

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