

# Beta-cell Insufficiency

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'Beta-cell failure' is a frequently used term to describe the structural and functional inability of the cells to fulfil their metabolic responsibility. This editorial reviews the anatomy and physiology of the beta cell, and describes factors which regulate this. The authors focus on semantics, comparing the phrases 'beta-cell failure', 'functional mass', and 'beta-cell insufficiency'. They suggest the use of 'beta-cell insufficiency', with descriptors such as 'partial' and 'complete', or 'reversible' and 'irreversible', to convey beta-cell dysfunction in type 2 diabetes. A three-phase taxonomic structure: beta-cell sufficiency, partial/reversible beta-cell insufficiency and complete/irreversible beta-cell insufficiency, is proposed as a tool to understand pathophysiology and facilitate therapeutic decision-making.

## Keywords

Beta-cell, insulin insufficiency, pancreas, pathogenesis, type 2 diabetes

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## Beta-cell anatomy

The beta-cell, perhaps one of the smallest endocrine glands in the human body, exerts the greatest influence on carbohydrate, and other nutrient, metabolism. The average adult human pancreas weighs slightly over 90 g, with wide inter-individual variation. It is much lighter as compared to other intra-abdominal structures such as the spleen (200 g) and kidney (2 x 150 g).<sup>1</sup> The islets of Langerhans make up 4.5% of the total pancreatic volume. Within these islets, beta-cells account for approximately 60–70% of the mass. Thus, beta-cells have a total weight of about 0.8 g in lean healthy adults, and 1.2 g in obese non-diabetic adults.<sup>2</sup>

## Beta-cell physiology

The beta-cell plays an essential role in metabolic homeostasis. It secretes insulin, an anabolic hormone which mediates glucose disposal. It is noteworthy that, though the human body contains a multitude of counter-regulatory or anti-insulin hormones, there is no 'back-up' hormone for insulin. While insulin-like growth factor 1 (IGF1) and other insulin like peptides do exist, they play no role in glucose metabolism. This may have been an evolutionary adaptation for early man, who lived in an environment characterised by food insecurity, where hypoglycaemia posed a greater potential threat than hyperglycaemia. Our modern lifestyle, with its characteristic overconsumption of calories and sedentary behaviour, poses totally opposite stresses.<sup>3</sup> To meet these challenges, the cell undergoes alterations in both structure (mass) and function (insulin secretion). However, when it is unable to cope with various insults, it reaches a stage of beta-cell exhaustion, which is followed by beta-cell 'failure'.<sup>4</sup>

## Diabetic beta-cell mass

Beta-cell mass is maintained by a balance between formation and apoptosis.<sup>5</sup> Creation of beta-cells can occur by various means, including differentiation, de-differentiation and regeneration.<sup>6</sup> In extremely stressful situations, alpha cells and ductal cells can transform into beta-cells, which are fully functional. On the other hand, beta-cells may undergo apoptosis, a caspase mediated form of regulated cell death (RCD).<sup>7</sup> RCD occurs in response to what are known as 'micro-environmental perturbations', and can be modulated, to some extent, by pharmacological and genetic means. The balance between formation and apoptosis of beta-cells is well regulated. No change in beta-cell mass is seen with ageing, even though the exocrine pancreas begins to atrophy after 60 years of age.<sup>2</sup> However, the nuclear diameter of the beta-cell, which is a surrogate marker of insulin secretion, increases in the face of age-mediated loss of insulin sensitivity.

Beta-cell mass increases with increasing body mass index, and may be 50% higher in overweight individuals. This enhancement of capacity is mediated by an increase in the number of beta-cells, rather than their size, and is also accompanied by increased secretion per cell.<sup>2</sup>

In persons with diabetes, similar changes in structure are noted. The beta-cell passes through five stages of progression, which are characterised by varying structural changes (see *Table 1*).

Table 1: Stages of beta-cell insufficiency

Stage	Description	Beta-cell mass	Beta-cell function	Glycaemic status	Proposed taxonomy	Treatment strategy
1	Compensation	Insulin resistance and/or decreasing beta-cell mass	Maintenance of differentiated function; normal GSIS	Normoglycaemia	<b>Beta-cell sufficiency</b>	Lifestyle
2	Stable state of beta-cell adaptation	Changes in beta-cell phenotype (gene and protein expression)  Loss of beta-cell mass or beta-cell hypertrophy (glucose-driven response stopping short of replication)	Diminished first phase GSIS  Secondphase GSIS partially preserved  Acute insulin responses to non-glucose secretagogues (isoproterenol, arginine) largely intact	Pre-diabetes	<b>Partial/reversible beta-cell insufficiency</b>	Lifestyle; insulin sensitisers
	Transient unstable period of early decompensation	Critical decline of beta-cell mass and/or increase in insulin resistance.	Insulin mRNA/function falls rapidly	Glucose levels rise relatively rapidly		Lifestyle; insulin sensitisers
	Stable decompensation	More severe beta-cell dedifferentiation  Beta-cell mass reduced to ~50% of normal	Reduced efficiency  Loss in insulin production	Frank diabetes		As per clinical situation Secretagogues may be used  Insulin, if required, will be short term
3	Severe decompensation	Profound reduction in beta-cell mass	Absent insulin production	Progression to ketosis	<b>Complete/irreversible beta-cell insufficiency</b>	Long-term insulin

GSIS = glucose-stimulated insulin secretion. Information source: Weir and Bonner-Weir, 2004.<sup>8</sup>

The first four stages are reversible, and the beta-cell can move in either direction, based upon environmental changes. The fifth stage, however, is irreversible.<sup>8</sup>

### Diabetic beta-cell function

These changes are also associated with functional impairment. Ageing glucose-tolerant adults are found to have impaired beta-cell function.<sup>9</sup> Both impaired degree, and delayed timing of insulin response to oral and intravenous glucose tolerance tests are noticed in persons with diabetes. Clinical studies also point to the frequent occurrence of beta-cell failure in persons with diabetes.<sup>10</sup>

Such functional dysfunction is found to be gradually progressive, and potentially reversible, in stages that correspond to the first four phases of structural impairment (see Table 1). The fifth and final phases of functional impairment are not reversible.

### A matter of words

When we use the term ‘failure’, however, it implies a functional failure, rather than an anatomical insufficiency. To communicate the importance of both structure and function, the term ‘functional mass’ has been used.<sup>11</sup> We prefer use of the word ‘insufficiency’. The dictionary defines the noun ‘insufficiency’ as the inability of an organ to perform its normal function.<sup>12</sup> This includes, or implies, both a structural and anatomic, and a functional or physiological defect. Therefore, this term represents the dysfunction of the pancreatic beta-cell more aptly.

### Classification of beta-cell function/mass

We may use adjectives or descriptors such as ‘partial’ and ‘complete’, or ‘reversible’ and ‘irreversible’ beta-cell insufficiency, to explain the five

phases of beta-cell dysfunction, as hypothesised by Weir and Bonner-Weir (see Table 1).<sup>8</sup>

Our three-phase taxonomic structure is much easier for clinicians (and person with diabetes) to understand and will help inform therapeutic decision-making as well. While persons with partial/reversible beta-cell insufficiency may benefit from interventions such as incretin-based therapy or nutrient load modulators, those with complete/irreversible insufficiency will certainly need insulin. This classification also helps plan insulin counselling. People with partial/reversible insufficiency (that is, beta-cell exhaustion) may be prescribed short-term insulin, with reasonable confidence that permanent injectable therapy will not be needed. On the other hand, persons with irreversible or complete beta-cell insufficiency will require long-term/indefinite insulin treatment.

Use of the word ‘insufficiency’ is also more desirable, as it appears innocuous and less judgmental. The word ‘failure’ has negative connotations, which may be extrapolated to the patient’s behaviour, the efficacy of the existing drug and the physician’s choice of therapeutic modality. ‘Insufficiency’ is an apposite choice to describe the clinical picture, as well as the beta-cell’s physical and physiological response to it.

We have used this terminology in discussion with patients, and find it a useful method of explaining diabetic pathophysiology in a simple and non-threatening manner. These words help create information equipoise, and facilitate shared decision-making, especially when insulin initiation is required in clinical practice. Avoidance of the word ‘failure’ prevents dejection and pessimism, and may limit diabetes distress as well.

## Summary

We propose a shift in semantics, from beta-cell failure (with its debate of loss of structure versus loss of function) to beta-cell insufficiency (with an integrated view of physio-anatomical defects). We also suggest a simplification of Weir and Bonner-Weir's hypothesis,

by creating an easier three-stage taxonomic model of beta-cell sufficiency, partial/reversible insufficiency, and complete/irreversible insufficiency. Such changes, though seemingly simple, will facilitate enhanced understanding, and greater clinical applicability, of this important concept. □

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