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Original hypothesis: Extracorporeal shockwaves as a homeostatic autoimmune restorative treatment (HART) for Type 1 diabetes mellitus

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SUMMARY

Mononuclear invasion of Langerhans islet and the ensuing insulitis triggers signal-transduction for the autoimmune mediated pancreatic beta-cell (β-cell) apoptosis that severely disrupts insulin production resulting in hyperglycemia associated with Type-1 diabetes (T1DM). Today extensive global research is being conducted to eliminate the need for insulin, and even prevent or find a cure for T1DM. The multifactorial combination of autoimmune dysfunction, Langerhans islet hypoxia, and bio-chemical disruption are seen to be contributory factors for β-cell destruction and the consequential disruption to insulin production. Regeneration of β-cells back to physiological levels may restore homeostatic insulin levels, reversing T1DM. Evidence suggests that there are still functioning pancreatic β-cells even in long standing T1DM providing the potential for their regeneration. Although the exact mechanism of extracorporeal shockwaves (ESW) is yet to be fully elucidated, it is seen to influence a complex spectrum of bio-chemical, cellular and neuronal functions (i.e. suppression of pro-inflammatory immune response, improved tissue hemodynamics, anti-microbial properties, and the induction of progenitor cell expression including proangiogenic factors and nitric oxide syntheses). The rationale for the use of ESW as a therapeutic modality in this instance is attributed to its restorative properties and safety profile demonstrated in urology, cardiology, chronic wounds, osteogenesis, complex pain syndromes, and tendinopathies. ESW may restore autoimmune homeostasis creating a suitable environment for pancreatic β-cell proliferation which in-turn may significantly increase or normalize endogenous insulin secretion reducing or totally eliminating dependency of exogenous insulin. The devastating complications, morbidity and mortality associated with T1DM warrants the exploration of homeostatic autoimmune restorative treatment (HART) modalities that may partially or fully reverse this disease condition. We present our hypothesis discussing ESW as a potential homeostatic autoimmune restorative treatment (HART) option for T1DM.

Introduction

A United Nations General Assembly resolution in 2006 recognized for the first time a non-communicable disease, namely diabetes mellitus (Type 1 and Type 2) as a global pandemic. Diabetes mellitus Type 1 (TIDM) is an autoimmune disorder that disrupts insulin production via the destruction of pancreatic β-cells (β-cells). The pancreas is a mixed gland containing both endocrine and exocrine components and functions. The endocrine component contains the islets of Langerhans that include: α-cells, β-cells, δ-cells and PP-cells that produce glucagon, insulin, somatostatin, and pancreatic polypeptide respectively. Insulin transmits signals to cells and tissue in the body to metabolize glucose to be utilized as fuel for energy. The absence or insufficient levels of insulin lead to the failure of glycemic homeostasis resulting in hyperglycemia. To date the exact etiology of TIDM is yet to be fully elucidated and there is presently no known method of preventing this autoimmune induced metabolic syndrome from occurring, neither is there a method for arresting or reversing this condition.

The multifactorial combination of autoimmune dysfunction, tissue hypoxia, and bio-chemical disruptions are all seen to be contributory factors for β-cell destruction and the consequential disruption to insulin secretion [1–4]. Although considered an

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autoimmune syndrome the development of T1DM does not necessarily require an exogenous or infectious trigger [5], suggesting a complex interplay of a constellation of genetic predisposition, aberrant cellular transcription and putative environmental events that gives rise to this metabolic syndrome [3,5–11].

Once triggered, the mononuclear invasion of Langerhans islet and the ensuing inflammation triggers signal-transduction for the autoimmune mediated (i.e. CD_{4+} & CD_{8+} Tcells) β-cell apoptosis that severely disrupts insulin production resulting in hyperglycemia [1,3,10,12–16], and the need for exogenous insulin dependence for survival. The consequence of sustained autoimmunity, inflammation and prolonged disruption to blood glucose homeostasis further triggers a complement chain of bio-cellular and molecular aberrances (i.e. poor hemodynamics, endothelial and neuronal dysfunction), that ultimately triggers the squela of neurological, cardiovascular, urological, and soft-tissue complications, that often results in the premature death of the sufferer [1,3,17–21]. To date the use of exogenous insulin therapy is the mainstay for insulin regulation in T1DM patients, and remains a lifelong life-sustaining therapy [18]. However exogenous insulin therapy is unable to compare with the precision of the innate endogenous insulin secretion regulated by β-cells [16] hence the subsequent long term sequelae of complications despite adequate glycemic control. This elucidates the fact that symptomatic management alone is ineffective for maintaining and protecting the patients' quality of life over the long term.

The incidence of T1DM continues to rise steadily with its incidence alarmingly expected to double, especially in children under the age of five by the year 2020 [22,23]. Given the present economic climate and outlook this statistic clearly indicates that interventions requiring life-long management are at risk of becoming unsustainable and hinder patients from being able to afford and access life-sustaining medications (i.e. insulin). Therefore, an urgent need for investigating potential homeostatic autoimmune restorative treatments (HART) becomes necessary in order to restore normative function and ensure economic viability.

Presently disease arresting or eliminating interventions are scarce and often require a high skill level, high cost and prolonged or sustained immune suppression. Some of these interventions are:

Organ transplantation and donor cell therapy

Pancreas transplant is one such method for disease elimination however; the scarcity of suitable donor organs, the continuous need for lifelong immune suppression, high skill level requirement, and the high cost associated with this procedure are factors that hinder its empirical availability [24,25]. The Edmonton protocol utilizing a combination of pharmacogenics and multiple donor pancreatic islets has proven to be successful. However, once again limited availability of suitable pancreatic islet donors, poor islet preservation capability, premature cellular necrosis and apoptosis, along with procedure and immunosuppressive risk are major drawbacks that limit the empirical use of this technique [18,26,27].

Stem cell therapy

Exogenous stem cell therapy has been attempted to replace β-cells however the inability to adequately control the underlying autoimmune response, associated the high cost again compromises the long term viability and efficacy of this procedure [21].

Pancreatic β-cell regeneration

Despite the sustained autoimmunity occurring in T1DM, there is still a continued presence of β-cells in the pancreas and the pancreatic duct even in long standing diabetes, which implies that there may still be a small amount of β-cell formation occurring via cell differentiation, or progenitor stem cell expression [3,28–30]. This provides a premise where targeted β-cell regeneration may be plausible. However, given the pathophysiology of T1DM where the dysfunctional autoimmune activity creates a self perpetuating environment for sustained ß-cell onslaught and destruction, any intervention that does not primarily address the autoimmune dysfunction may be a futile attempt in restoring insulin homeostasis.

The hypothesis

We hypothesize that extracorporeal shockwaves (ESW) is potentially a viable homeostatic autoimmune restorative treatment (HART) modality for T1DM that may regulate autoimmune aberrances allowing for a conducive environment for β-cell proliferation and survival, normalizing insulin secretion.

Extracorporeal shockwaves (ESW)

Shockwaves for biomedical use was first introduced for the eradication of urolithiasis, the world's first minimally invasive surgery, and the introduction of extracorporeal shock waves (ESW) into medicine [31]. Since the 90s ESW have been applied in orthopaedics, trauma and musculoskeletal medicine with successful results, and its application has since expanded into: sports medicine, pain management (CRPS1), arthropathy, chronic wounds, ulcer management, limb dystonia, neurologic disorders, cosmetic medicine, erectile dysfunction and cardiology [32–54]. In a recent exploratory investigation ESW was successfully in restoring peripheral insensitivity due to distal symmetrical peripheral polyneuropathy in a Type 1 diabetic foot, suggesting neuro modulatory benefits [35].

Shockwave propagation and mechanism of action

ESW may be propagated electro-hydraulically, electro-magnetically and piezo-electrically. Unlike ultrasound waves that are sinusoidal waves with a fairly long duration lifespan. ESW is a supersonic wave with a rapid rise time and a very short duration lifespan with peak pressure amplitudes reaching one hundred megapascals (MPa) within nanoseconds, and with its energy flux density levels (EFDL) measured in mj/mm^2.

Although the exact mechanism of action on tissue is yet to be fully elucidated, research indicate that ESW induces a constellation of bio-cellular and bio-chemical responses where structural and functional tissue plasticity are seen to occur in skeletal muscle, neuronal and connective tissue, epithelia and the endothelium [32–55]. ESW's are seen to trigger a localized cellular and bio-molecular response that improves regional and tissue hemodynamics, regulation endothelial nitric oxide synthese (eNOS), promote progenitor cell expression, increase collagen syntheses, mediate and regulate; pro-inflammatory substances, neurotransmitters, cytokine activity, transcription factor nuclear factor-kappa B (NF-κB) activation, and NF-κB dependent gene expression such as tumor necrosis factor alpha (TNF-α) and inducible NOS [32–56].

Evaluation and rationale of the hypothesis

Given the nature and the pathophysiology of T1DM as currently elucidated, the presence of sustained autoimmunity and inflammation, tissue hypoxia, and further biochemical disruptions result in

β-cell destruction causing exogenous insulin dependence. Some of the key factors involved in this syndrome are seen to be:

- Sustained autoimmune action maintained by factors such as: NF-κB, TNF-α, cytokines and other pro-inflammatory substances [3,5–11].
- Tissue hypoxia [2,4,26].
- Disruption to eNOS expression and function [17,57–59].
- Destruction of Langerhans islet β-cells [6–11,35]. However existence of β-cells are still evidenced in the pancreas [3,28–30] providing the premise for potentially stimulating proliferation.

Extracorporeal shockwave (ESW) treatment

As earlier elucidated the action of ESW on human tissue are many, and some of the bio-cellular responses induced by ESW may potentially return insulin homeostasis in T1DM patients. ESW is seen to modulate autoimmune (i.e. NF-κB, TNFα, iNOS etc.), inflammatory and cytokine activity (COX^2, IL-1B, IL-6 etc.), improve regional microcirculation, modulate eNOS activity, and enhance cell proliferation [32,34,36,37,39–43,46–56]. These mechanisms of action of ESW suggests that it may restore homeostasis of the autoimmune function, tissue hemodynamics, and regional nutrient bio-availability allowing for islet β-cell proliferation and ultimately homeostatic endogenous insulin secretion preventing the sequelae of complications of T1DM.

Testing the hypothesis

We propose the following investigations to be carried-out in two stages to test the hypothesis: in-vitro studies using islet β-cell lines to be tested. This will involve a control and treatment component where β-cells lines will be divided into treatment and control specimen groups. Treatment specimen group will be further divided into: (a) single treatment session group; and (b) three treatment session. All specimens groups will be incubated and monitored over several weeks. The objective of further diving treatment groups into a single treatment and multiple (×3) treatment groups is to determine if more than one session of ESW treatment would provide greater β-cell proliferation versus a single treatment. In-vitro cell culture studies will utilize proliferation assay and β-cell proliferation and apoptosis measurements. Our hypothesis suggests that the ESW treatment culture groups should reflect greater β-cell proliferation and survival compared to control, after which we would propose animal trails to commence. Our hypotheses does not include at this present moment utilization of ESW in combination with anti CD-3 and immune-regulatory agents, however this may be considered at a later stage.

Conclusion

The devastating complexity and the estimated rise in the incidence of T1DM warrants the exploration of modalities that are effective and sustainable to ensure quality of life and socio-economic wellbeing of our society. ESW may potentially be a HART modality that could improve quality of life and reduce the socio-economic burden associated with the global epidemic of T1DM.

Author contribution

K. Craig – Conceptualization, literature review, main author and manuscript submission.
C. D'Agostino – Literature review and article contributor.
D. Poratt – Literature review and article contributor.
M. Walker – Clinical research assistant.

Conflict of interest

None.

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