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REVIEW

Erythropoietin and diabetes mellitus

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Abstract

Erythropoietin (EPO) is a 30.4 kDa growth factor and cytokine that governs cell proliferation, immune modulation, metabolic homeostasis, vascular function, and cytoprotection. EPO is under investigation for the treatment of variety of diseases, but appears especially suited for the treatment of disorders of metabolism that include diabetes mellitus (DM). DM and the complications of this disease impact a significant portion of the global population leading to disability and death with currently limited therapeutic options. In addition to its utility for the treatment of anemia, EPO can improve cardiac function, reduce fatigue, and improve cognition in patients with DM as well as regulate cellular energy metabolism, obesity, tissue repair and regeneration, apoptosis, and autophagy in experimental models of DM. Yet, EPO can have adverse effects that involve the vasculature system and unchecked cellular proliferation. Critical to the cytoprotective capacity and the potential for a positive clinical outcome with EPO are the control of signal transduction pathways that include protein kinase B, the mechanistic target of rapamycin, Wnt signaling, mammalian forkhead transcription factors of the O class, silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*), and AMP activated protein kinase. Therapeutic strategies that can specifically target and control EPO and its signaling pathways hold great promise for the development of new and effective clinical treatments for DM and the complications of this disorder.

Key words: Protein kinase B; AMP activated protein kinase; Apoptosis; Autophagy; Forkhead; Metabolism; Factors of the O class; Diabetes mellitus; Erythropoietin; Stem cells; Silent mating type information regulation 2 homolog 1; Oxidative stress; Wnt1 inducible signaling pathway protein 1; Wnt

Core tip: Erythropoietin and the downstream signaling pathways of this cytokine that include protein kinase B, mechanistic target of rapamycin, Wnt signaling, Factors of the O class proteins, silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*), and AMP activated protein kinase offer new avenues for the development of novel treatments for diabetes mellitus and the complications of this disease.

Maiese K. Erythropoietin and diabetes mellitus. *World J Diabetes*

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ERYTHROPOIETIN: DISCOVERY AND BIOLOGY

The concept of circulating agents that travel throughout the body may have initially originated from Ernest Starling[1]. In 1905 at the Royal College of Surgeons, Sterling introduced the term "hormones", a term with Greek origins meaning to "excite" or "arouse", to depict the action of chemicals that are dispersed in the body and can target specific organs. Earlier work prior to the presentation by Sterling also described processes that could come under the description as being defined as "hormonal". Claude Bernard described the chemical release of glucose that was processed from glycogen in the liver[2]. Arnold Adolphe Berthold, another pioneer, also described messenger signals that could communicate among the different bodily organs[3].

Interestingly, almost as a counterpart to the discussions provided by Starling, Carnot *et al*[4] in 1906 presented the agent "hemopoietine". This agent was detected in the blood of rabbits after prompted by bleeding that led to the production of immature erythrocytes in untreated rabbits. Subsequent work by other investigators also showed that bled animals could result in prominent reticulocytosis in the plasma[5-7]. Later, the agent responsible for reticulocytosis was termed erythropoietin (EPO). EPO was linked to depressed oxygen levels and was shown to increase hemoglobin levels in parabiotic rat experiments when one of the two rats experienced hypoxia[8]. Subsequently, purification of the EPO protein in humans was achieved and cloning of the EPO gene fostered recombinant EPO (rhEPO) production for clinical treatments[9,10].

EPO is located on chromosome 7 and is a single copy in a 5.4 kb region of the genomic DNA[11]. The *EPO* gene encodes for a polypeptide chain that has initially 193 amino acids. A 27 amino acid hydrophobic secretory leader at the amino-terminal to result in a 166 amino acid peptide in the EPO protein is then cleaved[12]. Additional post-translational processing occurs with the removal of a carboxy-terminal arginine^{166} in the mature human and rhEPO to lead to a protein of 30.4 kDa with 165 amino acids[13-16].

EPO has four glycosylated chains that include three N-linked and one *O*-linked acidic oligosaccharide side chains[17]. The *N*-linked glycosylation sites are at aspartate^{24}, aspartate^{38}, and aspartate^{83} and the *O*-linked glycosylation site is at serine^{126}. Both the production and secretion of the mature EPO protein is dependent upon *N*- and *O*-linked chain integrity[18]. Replacement of asparagine^{38} and asparagine^{83} by glutamate or the replacement of serine^{126} by glycine can impair EPO production and secretion[19].

Several factors determine the biological activity of EPO[20]. The two disulfide bonds formed between cysteine^{7} and cysteine^{160} as well as cysteine^{29} and cysteine^{33} control the function of EPO[21]. EPO biological activity is lost with reduction of these disulfide bonds and with alkylation of the sulfhydryl groups. Almost 85% of EPO biological activity is restored with re-oxidization of EPO after reduction by guanidine[22]. In addition, EPO biological activity is maintained by the by the glycosylated chains[23] and EPO stability is fostered by the carbohydrate chains[24]. Free radical degradation of EPO is limited by both the glycosylated chains[23] and the oligosaccharides[25].

Currently, erythropoiesis-stimulating agents including EPO are approved for the treatment of anemia that results from chronic kidney failure, chemotherapy, human immunodeficiency virus, and to limit the number of blood transfusions for surgery[21,26]. The principal source for the production and secretion of EPO are the kidney peritubular interstitial cells[27]. Other organs that include the brain, uterus, and liver are also responsible for EPO production and secretion[17,27-30]. Expression of EPO is controlled by changes in oxygen tension and not by the concentration of red blood cells[28,31,32]. Hypoxia-inducible factor 1 (HIF-1) can control EPO expression and the EPO receptor (EPOR) to increase the production of EPO[11,28,33,34]. EPO and EPOR gene transcription occurs following HIF-1 activation. This gene transcription is governed by the transcription enhancer region in the 3'-flanking region of the EPO gene that binds to HIF-1[11,14]. HIF-1 also can foster pathways that provide cellular protection against injury[35-37]. Of note, EPO also can be generated from stimuli that may not directly involve hypoxia. During maturation of the brain that may be exposed to various toxic elements, EPO blood levels may be elevated and associated with greater disability[38]. Elevated EPO serum concentrations have been reported following xenon anesthesia in cardiac surgery[39]. Agents that decrease inflammation in cerebral microglia have been recently shown to lead to the release of EPO[40] and infection with malaria can result in significant serum levels of EPO[41]. Under some conditions during chronic hyperglycemia in adults, EPO levels may be depressed[42]. Conversely, EPO in the amniotic fluid of diabetic patients can be elevated and be suggestive of perinatal complications[43]. Furthermore, trophic factors such as insulin can stimulate EPO production in specific cells such as astrocytes[44].

EPO, OXIDATIVE STRESS, AND CELL SURVIVAL

As a cytoprotective agent, EPO promotes cellular survival, at least in part, through the control of oxidative stress mediated cell injury[45,46]. Reactive oxygen species (ROS) are released during oxidative stress[47]. This in turn can cause mitochondrial injury, DNA damage, and

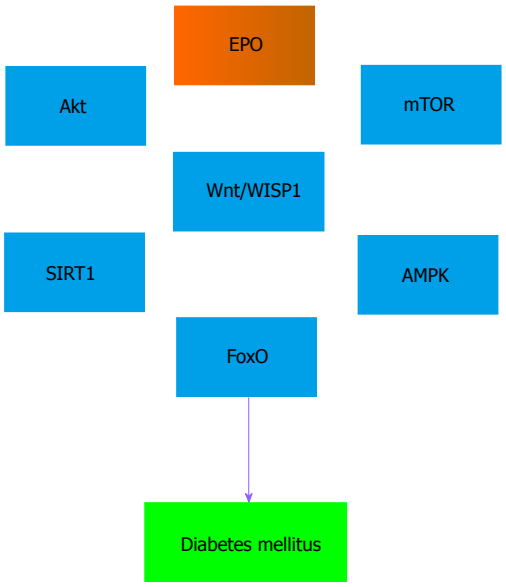

Figure 1 Erythropoietin signal transduction pathways that can lead to clinical benefit during diabetes mellitus. EPO governs a number of signal transduction pathways that involve protein kinase B (Akt), the mechanistic target of rapamycin (mTOR), Wnt and WISP1 signaling, mammalian forkhead transcription factors of the O class (FoxO), silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae) (SIRT1), and AMP activated protein kinase (AMPK). EPO: Erythropoietin; Akt: Protein kinase B; mTOR: Mechanistic target of rapamycin; FoxO: Factors of the O class; SIRT1: Silent mating type information regulation 2 homolog 1 (Saccharomyces cerevisiae); AMPK: AMP activated protein kinase.

protein misfolding[48-52].

Following the generation of ROS, cell death pathways of programmed cell death can ultimately determine cell survival[53-62]. Two particular pathways of programmed cell death involve autophagy[50,63-65] and apoptosis[15,55,57,66,67]. EPO prevents autophagic cell injury in glomerular mesangial cells during lipopolysaccharide exposure[68]. Administration of EPO also limits excessive autophagy that precedes apoptosis during experimental neonatal necrotizing enterocolitis[69]. During hyperoxia exposure and oxygen toxicity to the developing rodent brain, EPO has been shown to modify the activity of autophagy and limit neonatal brain damage[70].

In regards to apoptotic cell death, EPO prevents apoptotic injury during oxidative stress in endothelial progenitor cells[71] and attenuates neuroinflammation that can result in apoptosis[72]. EPO can assist with erythroid differentiation and prevent cellular apoptosis[73] as well as promote ventricular-subventricular zone neurogenesis and oligodendrogenesis[74]. Derivatives of EPO, such as glutaraldehyde-EPO, can protect renal cells from apoptosis during ischemia/re-perfusion injury and oxidative stress[75]. Administration of EPO also can block apoptotic cell death during neuronal kainate-induced oxidative stress[76], wound injury[77], vascular oxygen-glucose deprivation[78-80], loss of protective zinc finger transcription factors[81], anoxia[82-84], astroglial glutamate toxicity[85], beta-amyloid (Aβ) toxicity[86-90], renal adriamycin-induced nephropathy[91], ischemic brain injury[92], and multi-organ dysfunction induced by thermal injury[93]. In addition, EPO is protective against retinal disease[94], sepsis[95,96], advanced glycation endproducts (AGEs) exposure in Schwann cells[97], elevated glucose[78,98-102], free radicals[103-108], and toxins that lead to microglial injury[30,40,90,94,109].

SIGNAL TRANSDUCTION PATHWAYS FOR EPO

EPO cytoprotection is tied to a number of cell pathways[3]. In particular, phosphoinositide 3-kinase (PI 3-K) and protein kinase B (Akt) can lead to increased cellular survival with EPO (Figure 1). PI 3-K phosphorylates membrane lipids and controls Akt transition from the cytosol to the plasma membrane. Phosphorylation of Akt occurs at serine^{473} and threonine^{308} by phosphoinositide dependent kinase (PDK) PDK1 and PDK2[110-112]. EPO leads to Akt phosphorylation on serine^{473} to activate this kinase. EPO uses the Akt pathway to protect against autophagy and apoptosis injury in gastrointestinal disease[69], maintain vascular integrity and reduce inflammation[113], limit Aβ toxicity in microglia and neurons[90,114-116], reduce injury from sepsis[95,117], increase survival in cardiomyocytes during cardiac hypoxic/re-oxygenation injury[118], and block oxidative stress injury[78,82,104,105,119-122]. Akt in conjunction with EPO also improves the function of cells. For example, EPO activates Akt to increase the adhesive properties of endothelial cells and improve the vasculogenic potential of peripheral blood mononuclear cells[123].

The mechanistic target of rapamycin (mTOR) is closely linked to PI 3-K and Akt[124] (Figure 1). mTOR is a 289-kDa serine/threonine protein kinase that is encoded by a single gene *FRAP1*[124,125]. mTOR is important for the function of mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2)[126-129]. Neurons are protected against sepsis during exposure to EPO and activation of mTOR[95]. EPO prevents microglial cell injury through mTOR activation during oxidative stress[109] and Aβ toxicity[90]. During oxygen-glucose exposure in neurons, EPO affects multiple pathways of mTOR signaling[130] to include Akt and proline rich Akt substrate 40 kDa (PRAS40) to increase neuronal survival[79]. EPO and mTOR are required for the differentiation of neural precursor cells[131] and to control bone homeostasis with osteoblastogenesis and osteoclastogenesis[132]. EPO through mTOR can mediate resistance to hypoxia and oxidative stress in retinal progenitor cells[133] and also protect against increased activity of autophagy in epithelial cells[69]. Activation of mTOR prevents the induction of autophagy by phosphorylating autophagic related genes (*Atg*) and proteins that include Atg13 and ULKs to inhibit the UNC like kinase complex ULK-Atg13-FIP200[128]. Under some conditions, the concentration of EPO and activity of mTOR may be important for the degree of cellular protection that can be achieved. Elevated concentrations of EPO have been reported to lead to decreased phosphorylation and activity of mTOR

with increased apoptotic cell death[134]. Increased mTOR activity also is tied to tumor cell growth[135-138].

Closely associated to the protective pathways of Akt and mTOR are the wingless pathways of Wnt proteins[139] (Figure 1). Crosstalk occurs among Wnt signaling pathways, Akt, and mTOR[140] to foster cellular survival during Aβ toxicity[141,142], reduce cerebral ischemia[143,144], promote progenitor cell activation during intestinal inflammation[145], prevent neuronal cell loss[146], limit 6-hydroxydopamine toxicity[147], enhance microglial and macrophage survival and function[148,149], and increase tissue fibrosis[150]. EPO employs the Wnt pathway to lead to cellular protection. During renal ischemia and reperfusion, EPO limits tubular cell apoptosis by increasing the expression of Wnt7b and β-catenin as well as by down-regulating specific micro-RNAs (miRNA)[151,152]. Through Wnt1, EPO protects against elevated glucose exposure in cerebral endothelial cells and maintains the expression of Wnt1[100]. In addition, EPO uses Wnt signaling to prevent immune cell loss during oxidative stress[109], prevent Aβ toxicity in microglia[90], limit the activity of forkhead transcription factors that result in apoptosis[99,153], and maintain the survival of mesenchymal stem cells[154]. Of note, both EPO and the pathways of Wnt signaling are proliferative in nature and have the potential to lead to tumorigenesis. For example, prolonged exposure of growth factors such as EPO that rely upon Wnt signaling can result in inflammation, blood-brain barrier injury[155], and tumor growth[156-158].

Cellular protection with EPO that relies upon Wnt signaling also can be associated with the modulation of mammalian forkhead transcription factors[159]. Mammalian FOXO proteins are assigned to the O class of the forkhead box class transcription factors[160,161] (Figure 1). These transcription factors consist of FOXO1, FOXO3, FOXO4, and FOXO6 and exist throughout the body[162]. FoxO proteins can impact cellular survival[163] and are homologous to DAuer Formation-16 (DAF-16), a transcription factor in *Caenorhabditis elegans*, that leads to lifespan extension and affects insulin signaling[164,165]. Under many circumstances, the activation of FoxO proteins results in apoptotic cell death[153]. FoxO3a expression increases in the hippocampus during cerebral ischemia[166] and FoxO3a may lead to cell cycle induction that can promote neuronal apoptotic cell death[167]. Loss of FoxO3a expression and prevention of nuclear shuttling of FoxO3a in microglial cells and neurons results in increased survival during oxidative stress[146,148]. Inhibitory phosphorylation of FoxO3a and the nuclear export of FoxO3a during periods of elevated glucose also protects vascular cells[80,99,168,169] and neuronal cells[170].

In endothelial cells, EPO uses Wnt1 to block FoxO3a activity and maintain cerebral endothelial survival during elevated glucose[99]. Without Wnt signaling, EPO also has been shown to phosphorylate FoxO3a and lead to its inactivation to block apoptosis in neuronal cells[73]. EPO can prevent endothelial cell injury during oxygen-glucose deprivation by preventing FoxO3a nuclear subcellular trafficking that would lead to "pro-apoptotic" protein transcription and translation[20,80]. EPO can oversee stem cell proliferation through FoxO protein regulation. Through the control of FoxO3a activity, EPO promotes the development of erythroid progenitor cells[57,73,171,172].

FoxO protein activity is controlled by post-translation protein modifications that involve phosphorylation, ubiquitylation, and acetylation[162,173]. In regards to acetylation, FoxO proteins are deacetylated by histone deacetylases that includes the silent mating type information regulation 2 homolog 1 (*Saccharomyces cerevisiae*) (SIRT1)[54] (Figure 1). SIRT1 deacetylation of FoxO proteins can influence autophagic pathways such that glucose deprivation leads to increases in autophagic flux that maintain left ventricular function during periods of starvation[174]. SIRT1 may be required to promote cortical bone formation with osteoblast progenitors by deacetylation of FoxOs and preventing FoxO protein binding to β-catenin to inhibit Wnt signaling[175]. However, the degree of SIRT1 expression in relation to FoxO protein activity may be a significant determinant for cellular survival[160,161]. For example, during exercise a controlled up-regulation of FoxO3a and SIRT1 expression in cardiac tissue may be important to improve cell survival[176]. During oxidative stress, cell injury may be reduced with catalase expression regulated by FoxO1a expression and SIRT1 levels less than 7.5-fold. However, decreased cardiac function and apoptotic cell death in cardiomyocytes can ensue with elevated SIRT1 levels of 12.5-fold[177]. FoxO proteins, such as FoxO1, also can control SIRT1 transcription and increase SIRT1 expression[178]. Under some circumstances, SIRT1 and FoxO proteins may function synergistically to promote cell survival. Loss of the forkhead transcription factors FoxO1 and FoxO3 in combination with decreased SIRT1 activity during oxidative stress leads to a reduction in autophagy with chondrocyte cell death, demonstrating that SIRT1 with FoxO proteins may be required for cellular protection[179]. SIRT1 also has been shown to increase lifespan in higher organisms and offer protection against oxidative stress[180]. EPO relies upon SIRT1 activity to prevent cell injury during oxidative stress and elevated glucose[181]. EPO can raise cellular activity of SIRT1 and promote the subcellular trafficking of SIRT1 to the nucleus to protect endothelial cells during oxidative stress[80]. EPO is able to maintain adipose cell energy homeostasis and protect against metabolic disorders through SIRT1[101]. Pathways that involve Wnt signaling with the CCN family member Wnt1 inducible signaling pathway protein 1 (WISP1)[139] also require up-regulation of SIRT1 activity to block apoptotic pathways controlled by FoxO proteins[182] (Figure 1). WISP1 can increase neuronal survival by limiting FoxO3a activity and FoxO3a deacetylation, blocking caspase 1 and 3 activation, and promoting SIRT1 activity and trafficking to the cell nucleus[146].

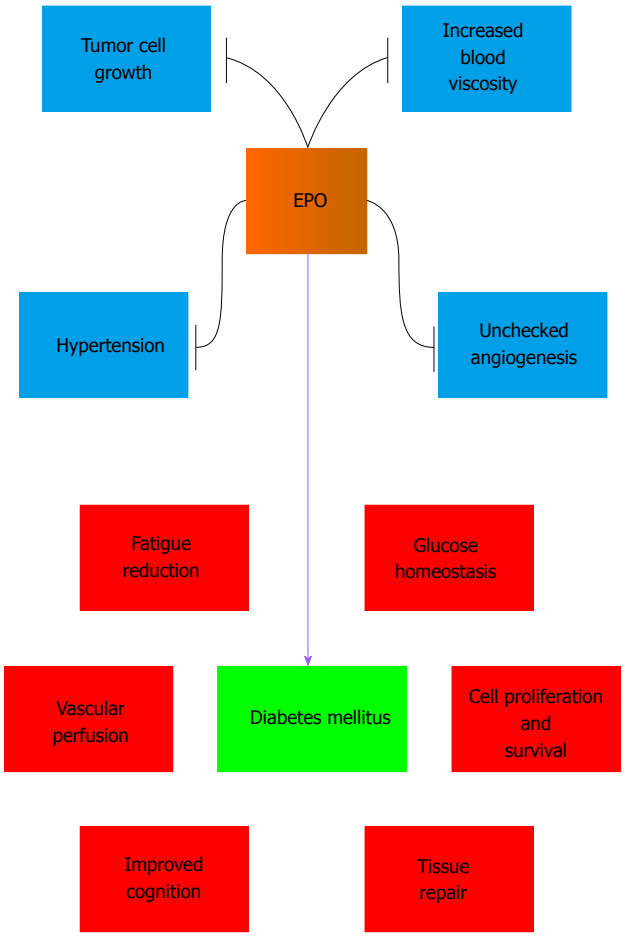

Figure 2 Targeting erythropoietin involves a balance that fosters clinical improvement over clinical disability. EPO can play a significant role in reducing disability and fostering clinical benefit during diabetes mellitus. Through its signal transduction pathways, EPO may improve organ and tissue function, reduce fatigue, improve vascular perfusion, maintain glucose homeostasis, assist with wound and tissue repair, and promote cellular proliferation, differentiation, and survival. However, the detrimental effects of EPO that can include tumor cell growth, hypertension, increased blood viscosity, and unchecked angiogenesis must be considered and eliminated for successful therapeutic treatments against diabetes mellitus. EPO: Erythropoietin.

NOVEL AVENUES FOR EPO AND METABOLIC DISEASE

Growth factors such as EPO offer potentially new treatment approaches for numerous disorders, but given the signal transduction pathways that are regulated by EPO, this agent provides exciting prospects for the treatment of diabetes mellitus (DM)[16,45]. DM affects at least 350 million individuals worldwide[182] and is increasing in incidence[183]. Of potentially greater concern are the numbers of undiagnosed individuals that just in the United States alone may exceed 8 million individuals who are believed to suffer from metabolic disorders[32,184,185]. DM can affect the entire body and involve the immune system[63,77,181,186-190], liver[55,191-196], musculoskeletal function[197-201], kidney[202-206], and cardiovascular system[163,188,207-213] to result in endothelial cell dysfunction[15,16,99,100,168,214,215] and atherosclerosis[45,67,199,216]. These disorders can easily affect other regions of the body such as the nervous system to lead to cognitive loss[14,217-219], visual deterioration[32,119,220,221], peripheral nerve disease[55], and ischemic disease of the brain[23,49,67,222-224].

EPO as well as its downstream pathways have been shown to have a high potential to treat multiple complications of DM[32] (Figure 2). In earlier work that examined diabetics and non-diabetics with severe congestive heart failure, EPO increased left ventricular ejection fraction, reduced fatigue, and lessened duration of hospital stay[225]. In patients with Type 1 DM and cognitive impairment related to hypoglycemia, administration of EPO leads to improvement in complex reaction time task assessing associated with attention and working memory[226]. EPO also could provide a small improvement to treat fatigue in patients with Type 2 DM and chronic kidney disease[227].

In experimental models of DM, EPO can reduce blood glucose levels in animal models of DM and obesity[228], protect against the detrimental effects of obesity in animal models[16], treat diabetic peripheral neuropathy[229], and block apoptosis in Schwann cells mediated by AGEs[97]. EPO has been shown to limit high glucose-induced oxidative stress in renal tubular cells[230], control cellular mitochondrial function[76,80,103,109,118], and maintain energy metabolism[15]. Through anti-inflammatory mechanisms and the blockade of apoptosis, EPO can protect pancreatic islet cells in models of type 1 DM and Type 2 DM[98]. Intravitreal administration of EPO in rodent models of DM can normalize gene expression that can lead to apoptotic and inflammatory cell death[231]. EPO is cardioprotective in DM models with the inhibition of glycogen synthase kinase -3β (GSK-3β)[232] that can limit Wnt signaling pathways[233]. Through increased angiogenesis and decreased apoptotic cell death, EPO can improve wound healing and wound closure in diabetic mice[77,234]. In vascular disease, EPO has been reported to protect the neuroglialvascular unit in a model of retinal neurodegeneration and secondary vasoregression[119]. EPO can directly protect against endothelial cell apoptosis during elevated glucose through activation of Wnt1[100] and the inhibition of GSK-3β and FoxO3a[99]. Improvement in vascular perfusion by EPO[123] also may afford indirect protection to assist with cognitive repair[235] and decrease peripheral nerve injury during DM[102].

Not all studies demonstrate a beneficial effect with EPO during DM, suggesting that focus upon the downstream signaling pathways of EPO with mTOR, Wnt signaling, FoxO proteins, and SIRT1 may yield greater utility for some clinical populations with complications of DM. In patients with DM and renal disease, EPO administration results in a two-fold increase in stroke that is not attributed to any baseline characteristic or to blood pressure, hemoglobin, platelet count, or treatment dose of EPO[236]. In mice that overexpress EPO, blood viscosity has been reported to be increased with a reduction in cerebral blood flow[237]. As a result, EPO may increase the risk for stroke through increased blood viscosity. Although

systemic administration of EPO may block retinopathy in animal models[94], elevated EPO concentrations in patients with DM also may lead to proliferative diabetic retinopathy[238] that could be associated with excessive vascular growth. EPO can increase vascular responsiveness[239] and may lead to hypertension[26,57,240]. Sustained erythrocytosis with agents such as EPO may result in the activation of inflammatory pathways and blood-brain barrier dysfunction[155]. As a proliferative agent, EPO also can lead to new tumor growth as well as foster the progression of existing tumors[156-158,241].

The potential adverse effects of EPO may be avoided by targeting more specific pathways controlled by EPO such as mTOR and AMP activated protein kinase (AMPK)[40,208] (Figure 2). AMPK oversees the activity of the hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex that is an inhibitor of mTORC1[135]. Metformin, an agent that controls hyperglycemia in DM, can reduce cardiomyopathy in experimental models of DM through AMPK activation[242]. EPO as well may dependent upon AMPK to promote antioxidant gene expression[243]. Furthermore, other EPO signaling pathways play a role in controlling AMPK. AMPK can increase nicotinamide phosphoribosyltransferase levels during glucose limitation resulting in elevated nicotinamide adenine dinucleotide[244] and lower levels of the SIRT1 inhibitor nicotinamide[245]. SIRT1 and AMPK activation promotes autophagy that offers endothelial cell protection during exposure to oxidized low density lipoproteins that can lead to atherosclerosis[246]. WISP1, a component of Wnt signaling, also controls the post-translational phosphorylation of AMPK that is involved in glucose homeostasis[124,247-249]. WISP1 regulates AMPK activation by decreasing phosphorylation of TSC2 at serine^{1387}, a target of AMPK, and increasing phosphorylation of TSC2 at threonine^{1462}, a target of Akt[142]. The ability of WISP1 to modulate AMPK activity is vital for the regulation of cellular metabolism during DM[249]. AMPK activity is able to reduce insulin resistance and lessen oxidative stress through activation of autophagy[200]. AMPK can prevent myocardial ischemia in experimental models of DM[250], assist with proper metabolic function of cells[251], and limit adipocyte differentiation, lipid accumulation, and obesity[252]. Yet, similar to SIRT1, the degree of AMPK activity is a significant consideration in DM. AMPK activation can lead to apoptosis in pancreatic islet cells in some experimental models of Type 2 DM[253].

CONCLUSIONS AND FUTURE PERSPECTIVES

In the global population, DM is a significant cause of disability and death. Treatment options to limit the onset and progression of this disease are insufficient and warrant the development of novel treatments. EPO, as a cytoprotective agent that controls a broad array of signal transduction pathways offers exceptional promise for the treatment of DM and pathways of oxidative stress. EPO has been shown in diabetic patients to improve cardiac function, reduce fatigue, and improve cognition. In experimental models of DM, EPO can reduce blood glucose levels, limit peripheral neuropathy, maintain mitochondrial function and energy metabolism, and block programmed cell death in many cell types such as Schwann cells, endothelial cells, neurons, pancreatic islet cells, and cardiomyocytes.

However, several challenges exist to move EPO forward as an effective treatment for DM. EPO has been reported to increase the risk of stroke in patients with DM and renal disease and has been demonstrated to increase blood viscosity in animal studies. EPO may be contraindicated in hypertensive patients and may contribute to elevated mean arterial blood pressure. Elevated concentrations of EPO have been linked to proliferative diabetic retinopathy that may be associated with excessive microvascular angiogenesis. Finally, EPO, as a growth factor and proliferative agent, may lead to new tumor growth and also promote the growth of existing tumors, especially in the treatment of patients with cancer and anemia.

Further investigations that assess the protective capacity of EPO and limit any potential detrimental clinical outcomes are warranted. New work has been directed to improving the molecular stability, solubility, and immunogenicity of EPO for improved therapeutic strategies to treat the complications of DM. Glycoengineering, a method that introduces N-linked glycosylation consensus sequences into proteins to increase serum half-life and biological activity, has been examined for EPO[254]. Darbepoetin alpha is one such example of a hyperglycosylated EPO derivative. Darbepoetin alpha has an increased serum half-life when compared to recombinant EPO[255] and is considered more potent than recombinant EPO[256]. EPO mimetic proteins are other avenues being pursued that can be used to activate the EPOR, potentially increase treatment half-life and maintain potency when compared to EPO, and lessen immunogenicity[257,258]. For example, CNTO 530 has been shown to increase reticulocytes, red blood cells and total hemoglobin in β- thalassemic mice[259].

A promising investigative course also could target the downstream signaling pathways of EPO that include Akt, mTOR, Wnt signaling, FoxO proteins, SIRT1, and AMPK. EPO employs Akt and mTOR for stem cell maintenance and differentiation, resistance against oxidative stress, and the regulation of autophagy. In experimental models of DM, EPO relies upon Wnt signaling, β-catenin, and the inhibition of GSK-3β to block apoptotic cell death. EPO also governs FoxO proteins and SIRT1 to protect against DM apoptotic vascular injury, maintain adipose cell energy homeostasis, and modulate autophagic flux to improve cardiac function during metabolic disturbances. Pathways that involve EPO and AMPK also offer interesting targets to maximize clinical efficacy and minimize unwanted side effects. AMPK reduces insulin resistance and lessens oxidative stress through

activation of autophagy, prevents myocardial ischemia in models of DM, and limits adipocyte lipid accumulation and obesity. WISP1 controls AMPK activity for the regulation of cellular metabolism during DM. In addition, SIRT1 and AMPK in conjunction with SIRT1 can increase autophagy activity to provide endothelial cell protection during exposure to oxidized low-density lipoproteins. However, it should be noted that consideration of these pathways may still require use of EPO or an EPO analogue since therapeutic success may be dependent on modulation of more than one of these down-stream pathways of EPO. In addition, one needs to emphasize that each of these pathways also can lead to undesirable biological outcomes under some circumstances such as tumorigenesis, pancreatic islet cell death, and cardiac dysfunction. Carefully targeting future investigations for EPO and its relevant signal transduction pathways for specific clinical disturbances of DM should offer the greatest promise for novel therapeutic strategies.

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REVIEW

Whey protein: The "whey" forward for treatment of type 2 diabetes?

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Abstract

A cost-effective nutritional approach to improve postprandial glycaemia is attractive considering the rising burden of diabetes throughout the world. Whey protein, a by-product of the cheese-making process, can be used to manipulate gut function in order to slow gastric emptying and stimulate incretin hormone secretion, thereby attenuating postprandial glycaemic excursions. The function of the gastrointestinal tract plays a pivotal role in glucose homeostasis, particularly during the postprandial period, and this review will discuss the mechanisms by which whey protein slows gastric emptying and stimulates release of gut peptides, including the incretins. Whey protein is also a rich source of amino acids, and these can directly stimulate beta cells to secrete insulin, which contributes to the reduction in postprandial glycaemia. Appetite is suppressed with consumption of whey, due to its effects on the gut-brain axis and the hypothalamus. These properties of whey protein suggest its potential in the management of type 2 diabetes. However, the optimal dose and timing of whey protein ingestion are yet to be defined, and studies are required to examine the long-term benefits of whey consumption for overall glycaemic control.

Key words: Whey protein; Postprandial glycaemia; Type 2 diabetes; Dietary intervention; Preload; Gastric emptying; Incretins; Gut hormones; Appetite; Amino acids

Core tip: Whey protein, a by-product of cheese-manufacture, shows promise in the dietary management of diabetes. Whey can slow gastric emptying, stimulate insulin and gut hormones including the incretins, and thereby reduce postprandial blood glucose, especially when consumed some minutes before a meal. Whey may also suppress appetite and reduce food intake. This review will summarise these properties of whey

and examine what further evidence is needed before whey can be recommended in the management of type 2 diabetes.

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INTRODUCTION

It is well established that the risk of microvascular, and to a lesser extent macrovascular complications of both type 1 and type 2 diabetes, is closely related to "average" glycaemic control as assessed by glycated haemoglobin (HbA1c). In people with type 2 diabetes who have relatively good glycaemic control, postprandial hyperglycaemia predominates over preprandial blood glucose in contributing to HbA1c[1,2]. Accordingly, focusing on postprandial glycaemia in patients with mild or moderate elevation of HbA1c is now appreciated as an important management strategy; indeed, achieving a "target" HbA1c of $\leqslant$ 7.0% is difficult without minimising postprandial glycaemic excursions[3,4]. The potential use of dietary manipulations to reduce postprandial glycaemia is intuitively appealing, particularly given the escalation in health care costs with the rising incidence of type 2 diabetes.

Whey, a by-product of cheese making, is gaining recognition as an important functional food[5]. Whey protein has been demonstrated to diminish postprandial glycaemia through various interrelated mechanisms including enhancement of insulin and incretin hormone secretion, slowing of gastric emptying, and reductions in appetite and energy consumption (Figure 1). These properties suggest the potential for whey in the management of type 2 diabetes. However, whey protein cannot be endorsed as a potential treatment until further studies show that it improves long-term glycaemic control without significant adverse outcomes.

This review will explore the different forms of whey protein and compare the effects of whey with other sources of protein in reducing postprandial glycaemia. It will address the mechanisms by which whey lowers glycaemia, the factors that need to be considered for optimal use of whey, and the effects of long term consumption of whey protein on glycaemic control, together with its potential adverse effects.

COMPARISON OF WHEY AND CASEIN PROTEINS

Milk proteins are an important amino acid source for young mammals; they facilitate uptake of nutrients and trace elements[6] and provide a source of bioactive peptides with a range of physiological functions[6-8]. Cow's milk contains about 3.5 g of protein per 100 mL, of which whey accounts for about 20% and casein 80%[9-11].

Whey consists of a heterogeneous group of proteins[12], including beta-lactoglobulin (35%), alpha-lactalbumin (12%), proteose peptone (12%), immunoglobulins (8%), and bovine serum albumin (5%)[11,13,14]. When chymosin is used in the cheese-making process, glycomacropeptide - which is high in branched chain amino acids - accounts for about 12% of total protein in whey[15]. Up to 1% of the total protein content of whey comprises "low abundance" proteins, including lactoferrin, and lactoperoxidase[14]. All these proteins have been reported to have nutritional and/or physiological functions[5].

Whey is seen as a more attractive protein for use as a dietary supplement compared to casein, due to differences in the amino acid composition and absorption kinetics between the two proteins[16]. Whey protein has a higher proportion of branched chain amino acids than casein[17], and is more soluble in the acidic environment of the stomach, leading to more rapid digestion[18] - hence it is termed a "fast" protein[19], while casein is a "slow" protein[16,20]. Using ^{13}C-leucine-labelled whey and casein protein, Boirie *et al*[18] demonstrated in healthy subjects that whey protein results in more rapid appearance, and higher peak plasma concentrations of amino acid, when compared with casein, while Stanstrup *et al*[21] reported that levels of amino acids after a fat rich meal containing whey were substantially higher when compared to the same meal containing casein. As a result of greater solubility, more rapid digestion, and resultant higher plasma concentrations of amino acids, whey appears to be the more favourable protein to provide nutritional and functional benefits.

FORMS OF WHEY PROTEIN - ISOLATE, CONCENTRATE AND HYDROLYSATE

Whey protein is available in three forms: concentrate, isolate, and hydrolysate. Whey protein concentrate contains 35%-80% protein, with fat, lactose and minerals making up the remainder; whey protein isolate contains 85%-90% protein and very little fat or lactose[5,15,22]; and whey protein hydrolysate consists of proteins that have undergone hydrolysis by proteolytic enzymes[14]. Whey hydrolysates and isolates are more costly than whey concentrates, which is an important consideration if whey protein is to be used for a prolonged period of time in the management of type 2 diabetes. It is therefore important to consider the evidence that one form of whey protein is more "functional" than another.

Protein hydrolysates are usually more rapidly absorbed than the intact protein[23], but since intact whey is already a rapidly digested protein, any difference is likely to be minimal[24,25]. Some studies have suggested that whey hydrolysates may stimulate insulin and glucose-dependent insulinotropic polypeptide (GIP) secretion to

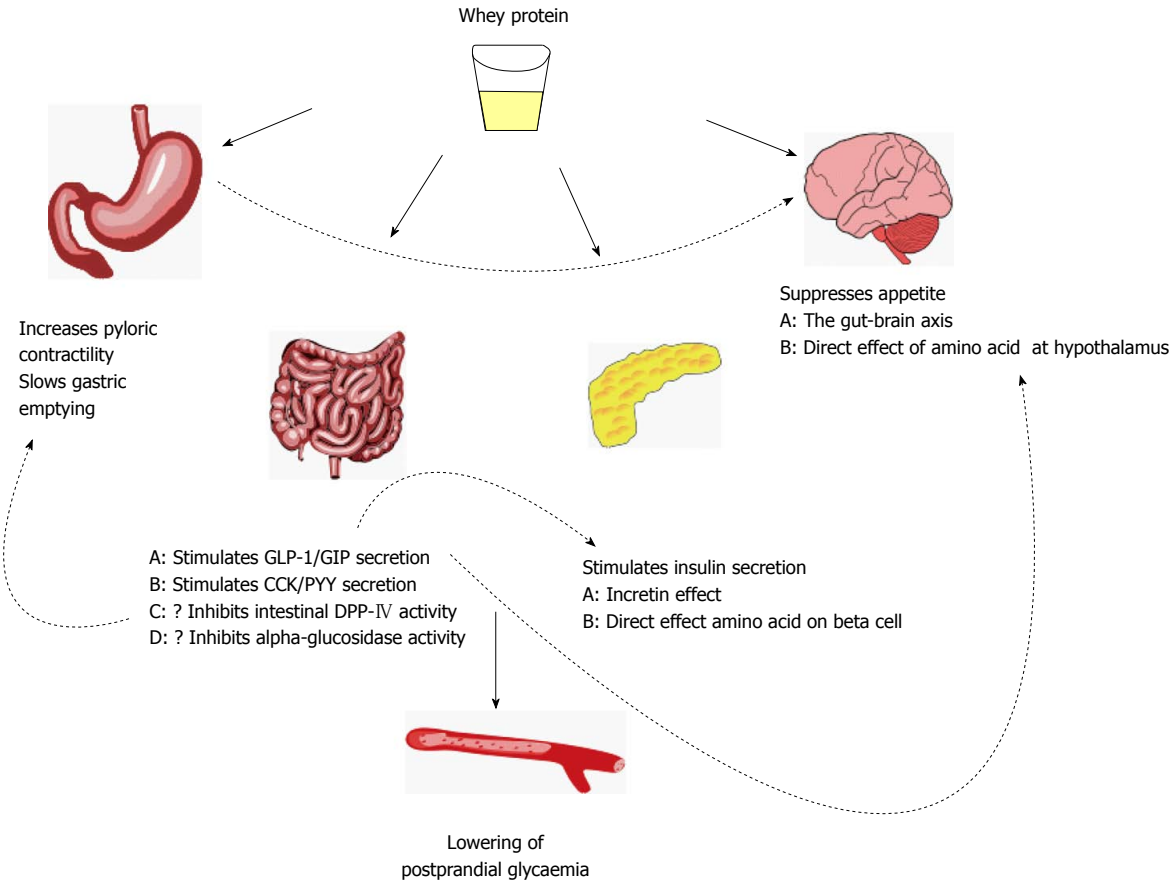

Figure 1 Mechanisms by which whey protein can reduce postprandial glycaemia. GLP-1: Glucagon-like-peptide-1; GIP: Glucose-dependent insulinotropic polypeptide; CCK: Cholecystokinin; PYY: Peptide YY; DPP-Ⅳ: Dipeptidyl peptidase-Ⅳ.

a greater degree than the intact protein[26,27]. Mortensen *et al*[28] investigated the effects of adding 45 g of four different whey protein formulations (whey hydrolysate, whey isolate, alpha-lactalbumin enhanced whey, and caseinoglycomacropeptide enhanced whey) to a high fat/carbohydrate meal in subjects with type 2 diabetes, and reported that the first phase insulin response (as assessed by the incremental area under the curve (iAUC) up to 30 min) was enhanced after whey hydrolysate compared with the other three supplements, and that whey isolate and whey hydrolysate yielded a greater overall insulin response (iAUC at 480 min) than the other two supplements, without any difference between them. Whey proteins which have been hydrolysed are, however, usually less palatable[29], which detracts from their potential therapeutic use. There is no compelling evidence that one form of whey protein is significantly more potent than another, particularly in relation to reduction of postprandial glycaemia, so consideration of palatability and cost must also be taken into account.

ROLE OF THE INCRETIN HORMONES, GIP AND GLP-1, IN PROTEIN-INDUCED INSULIN SECRETION

The phenomenon by which insulin secretion is increased when glucose is given by the enteral route, when compared to an isoglycaemic intravenous glucose infusion, is called the "incretin effect", and is attributed to the secretion of "incretin" hormones from the gut. The two known incretin hormones, glucagon-like-peptide-1 (GLP-1) and GIP, exert their insulinotropic actions through distinct G-protein-coupled receptors that are highly expressed on beta cells[30]. After oral glucose, about two thirds of the plasma insulin response can be attributed to the effects of GIP and GLP-1. The insulinotropic effects of both GIP and GLP-1 are glucose-dependent, requiring a substantial elevation of blood glucose (> 8 mmol/L) to be manifest[31]. Incretin based therapies, such as GLP-1 receptor agonists, are attractive for this reason, as insulin release is only triggered in the presence of elevated glucose concentrations, with consequently minimal risk of hypoglycaemia.

Incretin hormones may play an important role in protein-stimulated insulin release in health and type 2 diabetes[32]. GIP and GLP-1, when infused intravenously to mimic physiological increments after a meal, have been reported to potentiate the insulin secretory response to Ⅳ administration of an amino acid mixture[33]. In a study of oral administration of protein and amino acids in health, a whey drink resulted in a greater GIP response than a drink containing the essential amino acids found in whey, with an associated augmentation

of the insulin response[34]. Additionally, the stimulation of insulin secretion from murine islets *in vitro* by whey was inhibited by GIP receptor antagonists[35]. The effects of the GLP-1 antagonist, exendin 9-39, on whey-induced insulin secretion have not been evaluated. However, it is clear that the insulintropic effects of whey, at least in part, involve the incretin axis.

In humans, fats and carbohydrates are reported to be the most potent stimuli for GLP-1 and GIP secretion[36], although the effects of protein on incretin secretion are less well studied than the other macronutrients[37]. Nevertheless, whey protein is reported to stimulate GLP-1 and GIP release[17,34,35,38-40]. Bowen *et al*[41] showed that plasma active GLP-1 concentrations were higher after intake of a whey protein beverage compared to a glucose or fructose drink, but the mechanisms mediating protein-induced incretin secretion remain largely unknown[37].

Although the capacity for GIP to stimulate insulin is markedly diminished in type 2 diabetes, at least in part due to the effects of chronic hyperglycaemia[42], GLP-1 retains much of its activity. As whey protein can augment incretin hormone secretion and enhance protein-stimulated insulin release, it seems reasonable to view whey as a potential therapeutic agent in the treatment of type 2 diabetes.

ROLE OF GASTRIC EMPTYING IN MEDIATING THE EFFECTS OF WHEY ON POSTPRANDIAL GLYCAEMIA

It is now well established that gastric emptying plays a major role in determining postprandial blood glucose concentrations, particularly the "early" glycaemic response, and that slowing gastric emptying can diminish postprandial glycaemic excursions in health and diabetes[43-46]. In healthy humans, the addition of protein to oral glucose lowers postprandial blood glucose concentrations acutely, probably predominantly by slowing gastric emptying[47]. Similarly, a "preload" of whey has been shown to slow gastric emptying of a subsequent meal in both health[17], and in type 2 diabetes[48].

The effects of whey on gastric emptying, postprandial glycaemia, and the secretion of incretin hormones, are interdependent. The incretins not only have major insulinotropic effects, but GLP-1 also slows gastric emptying, suppresses energy intake and has glucagonstatic effects to improve postprandial glycaemia[42]. Reports that GLP-1 secretion is impaired in longstanding type 2 diabetes[49,50] did not take potential differences in gastric emptying rates into account; furthermore, it has now been shown that in patients with type 2 diabetes managed by diet or metformin only, the GLP-1 response to an intraduodenal glucose challenge is apparently normal[46]. That GLP-1 secretion is intact in type 2 diabetes adds to the rationale for using a nutritional approach to enhance the secretion of endogenous GLP-1. Moreover, gastric emptying and appetite are inhibited by gut hormones other than the incretins, including cholecystokinin (CCK) and peptide YY (PYY)[51-53]. Stimulation of these hormones by nutritional supplements could also be beneficial in reducing postprandial glycaemia.

ANTROPYLORODUODENAL MOTILITY

Interactions between nutrients and the small intestine can induce feedback on gut function to suppress antral motility and stimulate pyloric contractions, with resultant slowing of gastric emptying[54]. In both healthy young and older humans, intraduodenal delivery of whey suppresses antral and duodenal waves and increases isolated pyloric pressure waves. Such changes in antropyloric motility in response to nutrient ingestion also appear to be independently related to subsequent energy intake in healthy young subjects[55]. Soenen *et al*[56] examined the effects of intraduodenal whey protein infusion on appetite and subsequent *ad libitum* energy intake in relation to antropyloroduodenal motility. They reported that energy intake at a buffet meal was inversely related to the number of isolated pyloric pressure waves, and positively related to the number of antral pressure waves, supporting a relationship between antropyloroduodenal motor activity and feeding behaviour.

POTENTIAL IMPACT OF WHEY ON DIPEPTIDYL PEPTIDASE-IV

The incretin hormones are rapidly degraded to inactive metabolites by dipeptidyl peptidase-Ⅳ (DPP-Ⅳ). More than 50% of the GLP-1 newly secreted from intestinal L cells is degraded before reaching the systemic circulation[57], mainly by DPP-Ⅳ present in the endothelium of the capillary bed in close proximity to the L cells[36,57]. Whey hydrolysates, produced using digestive enzymes such as pepsin and trypsin, have been found to inhibit the activity of DPP-Ⅳ *in vitro*[58-61]. For rodents *in vivo*, ingestion of whey protein can reduce DPP-Ⅳ activity in the proximal small bowel, thereby increasing intact incretin hormone concentrations[62]. Further *in vivo* studies, particularly in humans, are required to confirm this phenomenon, and establish its durability with long term ingestion of whey[63].

EFFECTS OF WHEY ON ALPHA-GLUCOSIDASE

Alpha glucosidase is an enzyme that hydrolyzes starch and disaccharides to enable absorption of glucose at the small intestinal brush border. *In vitro* studies have shown that whey protein hydrolysate has a modest effect to inhibit alpha-glucosidase[59], which may be

clinically relevant given that alpha-glucosidase inhibitors, such as acarbose, are used widely in the management of type 2 diabetes to improve postprandial glycaemia. Human studies are required to further evaluate this mechanism and the magnitude of the glucose lowering effect attributable to it.

TIMING OF WHEY PROTEIN, "PRELOADS", AND GASTRIC EMPTYING

The concept of a "preload" refers to administration of a small load of macronutrient at a fixed interval before a meal, so that the presence of nutrients in the small intestine induces the release of GLP-1 and GIP, and other gut peptides such as CCK and PYY, to slow gastric emptying and stimulate insulin secretion in advance of the main nutrient load. In health, whey protein preloads have been shown to slow gastric emptying, as assessed by the plasma concentrations of oral paracetamol given with the meal, and enhance post-prandial GLP-1 levels[64]. Similarly, whey given immediately before a meal, with or without additional amino acids, reduces the postprandial glycaemic response by over a third (iAUC 0-60 min), associated with an increase in the early postprandial plasma insulin and GLP-1 responses[65].

The capacity for a whey preload to stimulate incretin hormone secretion and slow gastric emptying has also been established in subjects with type 2 diabetes[48]. Ma *et al*[48] reported in type 2 patients that a 55 g whey protein preload, given 30 min before a meal, slows gastric emptying when compared to either a nutrient-free preload or ingestion of whey with the meal. In this study, gastric emptying was quantified using scintigraphy, which represents the "gold standard". Whey protein markedly reduced postprandial glucose excursions (iAUC after whey preload about half that of control), and stimulated insulin and CCK, as well as GIP and GLP-1. Both the GLP-1 response and the reduction in postprandial glycaemia were greater when whey was given as a preload, when compared to ingestion with the meal. Accordingly, this study not only established that whey can slow gastric emptying substantially in type 2 diabetes, but that the timing of supplementation is pivotal to the stimulation of incretins and other gut hormones. These acute effects of whey preloads to improve postprandial glycaemia were recently confirmed in another study in type 2 patients[66]. While whey has been shown to slow gastric emptying acutely, it remains to be seen whether this effect is sustained with long term administration.

AMINO ACIDS AS A STIMULUS FOR INSULIN SECRETION

It has been established for many years that ingested protein stimulates insulin secretion[47,67], an effect observed in both healthy subjects and in those with type 2 diabetes. This effect is enhanced when protein is co-ingested with carbohydrates when compared with the ingestion of carbohydrate or protein alone, suggesting a synergy between oral protein and glucose[68-72]. In a recent comparison of four protein sources, the greatest postprandial insulin response was associated with whey compared to casein, gluten or cod, and was attributed to the more rapid appearance of amino acids in plasma when derived from whey[21].

Whey protein is a rich source of essential amino acids and branched chain amino acids known to have potent insulinotropic properties[73]. The branched chain amino acids - leucine, valine, and isoleucine - are more insulinogenic than other amino acids[40,74]. In the 1960s, Floyd *et al*[67,75,76] showed that amino acids, given either intravenously or orally, had the capacity to stimulate insulin secretion and reduce blood glucose concentrations. The insulinotropic effect of whey, at least in part, reflects a direct effect of amino acids to stimulate beta cells[35,77-80]; the underlying mechanisms are complex and involve mitochondrial metabolism[77].

Amino acids can stimulate insulin secretion in type 2 diabetes as well as in health. van Loon *et al*[81] reported that patients with long standing type 2 diabetes who co-ingested an amino acid/protein mixture (wheat protein hydrolysate) with a carbohydrate meal almost trebled their insulin response, when compared to ingestion of carbohydrate alone. This preserved stimulation of insulin by amino acids in type 2 diabetes contrasts with the diminished insulin response to carbohydrates, when compared with healthy controls. Similarly, addition of casein to carbohydrate has also been noted to potentiate insulin secretion in longstanding type 2 diabetes. That amino acids derived from ingested proteins remain a strong stimulus for insulin secretion, even in patients with long standing type 2 diabetes, supports their potential efficacy in the management of this condition[68].

ROLE OF GLUCAGON

Glucagon, secreted from the alpha cells of the pancreas, primarily acts on the liver to initiate glycogenolysis and gluconeogenesis, which then increases endogenous glucose production. Glucagon secretion is exaggerated in response to a meal in patients with type 2 diabetes[82], and ingested protein results in an increase in plasma glucagon levels[83]. It might therefore be expected that protein ingestion would increase blood glucose concentrations, but this is not necessarily the case.

Calbet *et al*[84] gave 6 healthy adults four tests meals containing glucose, cow's milk solution, pea and whey peptide hydrolysates, and found that the glucagon response was linearly related to the increase in plasma amino acids. Despite this, plasma glucose levels after whey hydrolysates decreased by about 1.5 mmol/L from baseline to 180 min, most likely due to the effects of insulin, which is stimulated concurrently and is particularly effective at suppressing glycogenolysis.

IS WHEY PROTEIN EFFECTIVE IN REDUCING POSTPRANDIAL GLYCAEMIA IN TYPE 2 DIABETES?

Although it is clear that whey has an insulinotropic effect, it is less clear as to whether the magnitude of insulin stimulation is sufficient to reduce postprandial glycaemia in patients with type 2 diabetes, who tend to be insulin-resistant, and often exhibit hyperinsulinaemia[40,85-87]. Insulin sensitivity, assessed using a euglycaemic-hyperinsulinaemic clamp, impacts on the capacity for acute administration of protein to reduce blood glucose concentrations in healthy subjects[88], and this may explain why some studies of patients with type 2 diabetes reported no reduction in blood glucose despite stimulation of insulin after a protein meal[38,89].

Frid *et al*[39] evaluated the effect of adding whey protein to high glycaemic index meals taken at breakfast and lunch in patients with type 2 diabetes. Plasma insulin responses were higher after both breakfast (31%) and lunch (57%) with whey (27.6 g) when compared to lean ham or lactose. There was a reduction in blood glucose excursions after lunch but not breakfast, which might be related to either the differing meal content, or to higher insulin resistance seen in the fasting state[90] affecting responses after breakfast.

Conversely, other studies in type 2 diabetes have reported up to 3 or 4 fold increases in insulin responses to meals containing protein and carbohydrate, when compared to carbohydrate alone, with concomitant reductions in postprandial glycaemia[71,91]. Nuttall *et al*[70] evaluated nine male subjects with diet controlled type 2 diabetes and showed that the blood glucose response (AUC) to protein and glucose ingestion was one third lower than after glucose alone, and the mean insulin AUC was also considerably greater. While these studies used beef or casein, whey is also effective for both stimulating insulin secretion and reducing postprandial glycaemia in individuals with type 2 diabetes and/or insulin resistance[48,92].

IS THE DOSE OF WHEY IMPORTANT?

When assessing the magnitude of glycaemic responses after whey protein consumption, one should consider not only the timing of ingestion (*e.g.,* whether giving as a preload), but also the dose, since the effects of whey on glycaemic responses, as well as appetite, appear to be dose-dependent[19,93]. Preloads of whey concentrate in doses of 5 g, 10 g, 20 g, and 40 g, and control, were given to 22 healthy individuals, followed 30 min later by a standardised pizza meal; the 20 g and 40 g whey preloads suppressed appetite more than control, or 5 g or 10 g whey protein, as assessed by visual analogue questionnaires[93]. In addition, whey protein reduced postprandial glucose in a dose-dependent manner. Poppit *et al*[94] gave 50 overweight women drinks containing 5 g, 10 g or 20 g whey, or control, 120 min after a standardized breakfast, and found that there was a tendency for hunger and fullness to be dose-related, although this did not reach statistical significance.

In healthy volunteers, whey protein taken with a meal increases insulin and reduces postprandial glycaemia in a dose-dependent manner[87]. Gunnerud *et al*[87] found that a drink containing 25 g glucose and either 4.5 g, 9 g or 18 g whey protein, reduced postprandial glycaemia (iAUC) by 25%, 37% and 46% respectively, compared to a 25 g glucose alone; the reductions with 9 g and 18 g whey were statistically significant. There was also a dose-dependent increase in insulin (iAUC 0 – 120 min), which reached statistical significance with the highest dose of whey.

While whey has convincing dose-dependent effects on glucose, insulin and appetite, the optimal dose for improving long-term glycaemic control in people with type 2 diabetes is yet to be determined.

WHEY AND APPETITE REGULATION

Reduction in energy expenditure and appetite may be achieved through manipulation of dietary macro-nutrient composition[95]. Protein has been shown to be more satiating than other macronutrients such as carbohydrate and fat[16,96], and has also been reported to increase satiety[97-99]. Whey protein, in particular, has been shown to enhance satiety and reduce food intake at the next meal in acute studies[93,100], and this effect is thought to be mediated by gut hormones[17,101], specifically by stimulation of CCK, PYY and GLP-1, and by suppression of the orexigenic hormone, ghrelin[16].

Bowen *et al*[95] reported prolonged postprandial suppression of ghrelin, and elevation of GLP-1 and CCK, after consumption of whey, gluten and soy based preloads compared with glucose, and this was associated with reduction of energy intake at an *ad libitum* meal. CCK is typically associated with satiation; however, in this study there was a trend for an inverse relationship between CCK and subsequent energy intake, which suggests that CCK can also contribute to satiety. Similarly, in a study where hunger scores were reduced after whey ingestion compared to casein, the CCK and GLP-1 responses were higher following whey, which may have contributed to its greater satiating effect[17]. Other studies have reported that PYY concentrations are higher after whey compared with other proteins, but with comparable CCK and ghrelin responses[64].

DIRECT EFFECTS OF AMINO ACIDS ON HUNGER

Elevation in plasma concentrations of amino acids after ingestion of whey may affect appetite[102,103] by hitherto poorly defined mechanisms, including vagal feedback and direct suppression of hunger at the level of the hypothalamus[104]. The greater suppression of hunger by whey, when compared to soy or casein, is associated

with increased concentrations of the amino acids leucine, lysine, tryptophan, isoleucine, and threonine[105]. Furthermore, tryptophan is synthesised into serotonin, which itself is known to influence food intake[103,106].

EFFECT OF WHEY ON ENERGY EXPENDITURE

Energy expenditure from thermogenesis, which increases oxygen consumption and body temperature, is thought to induce feelings of satiety[107]. Of the macronutrients, dietary protein stimulates thermogenesis and satiety more than carbohydrate or fat[103]. Acheson *et al*[108] reported that whey protein elicits a greater thermic response than protein composed of either casein or soy, where protein accounted for 50% of the energy content of the meal. This may be because whey protein, as a "fast" protein, is rapidly digested to result in greater postprandial protein synthesis[18]. In particular, leucine, which is present in high concentrations in whey[109], has been shown to stimulate muscle protein synthesis[110] and may also increase postprandial energy expenditure[109].

EFFECTS OF LONG TERM CONSUMPTION OF WHEY PROTEIN ON GLYCAEMIC CONTROL

High protein diets induce weight loss and preserve lean mass[111]. However, there is a paucity of data relating to whether whey has the capacity to reduce glycated haemoglobin with ongoing treatment in patients with type 2 diabetes.

A 5-wk study in 8 men with type 2 diabetes showed that a diet containing 30% *vs* 15% of total energy derived from protein, with a corresponding decrease in carbohydrate content, was associated with a greater (by about 0.5%) decrease in glycated haemoglobin[112]. In another study, 72 non-diabetic obese men were randomised to receive supplements of either whey protein isolate, casein, or glucose (each 54 g/d), 30 min before breakfast and the evening meal for 12 wk. Improvements in fasting insulin and homeostasis model assessment of insulin resistance score of almost 10% were observed with whey compared to control, but there was no difference in the fasting serum glucose[113].

In considering the use of whey protein in the management of diabetes, it is also important to recognise the potential adverse effects of longer term supplementation. There have been concerns that high protein diets could potentially reduce bone density and impair renal function. However, a recent two year weight loss study in postmenopausal women found no clinically significant effect of a high protein diet on bone density[114]; nor was there any reduction in renal function in a one year weight loss study in patients with type 2 diabetes with microalbuminuria, assigned to a high protein diet ($\geqslant$ 90 g protein/d)[111,115].

The effects of additional energy intake associated with protein supplements should also be considered if using this strategy over the long term. Subjects tend to compensate for the additional energy load by eating less at a subsequent *ad libitum* meal in acute and short term (5 d) studies[116,117]. This is supported by a 12-wk study in which overweight men received 54 g whey supplements per day, but showed no change in body composition[113]. Age may be an important determinant of this effect, however; Soenen *et al*[56] observed that older men (aged 68 to 81 years), had less capacity to compensate for the additional energy intake associated with whey administration when compared to young men.

Whey's ability to slow gastric emptying is one of the main mechanisms by which postprandial glycaemia is reduced acutely after a meal. However, it is unknown whether the capacity for whey to slow gastric emptying is sustained with prolonged exposure, or whether there is an adaption to this macronutrient of the gut feedback mechanisms that control gastric emptying, as has been demonstrated for carbohydrates and fats[118]. It would therefore be important to establish whether slowing of gastric emptying induced by whey is sustained with prolonged exposure; this appears to be the case over four weeks in a small pilot study[119].

CONCLUSION

The acute effects of whey protein on postprandial glycaemic excursions appear promising, but the long term efficacy and optimal application in the management of type 2 diabetes remain to be determined.

Patients most likely to benefit from postprandial glucose lowering by whey protein are those with mild to moderate elevation of HbA1c, who have relatively well controlled fasting glucose, since this is the group of patients in whom postprandial glycaemia makes the greatest relative contribution to HbA1c. However, combining a dietary strategy with pharmacological agents in less well controlled patients should also be evaluated, such as the combination of insulin to control fasting glucose, together with whey protein to reduce postprandial glycaemia; such a concept has proven to be effective with the combination of basal insulin and short-acting GLP-1 receptor agonists[120]. Moreover, the combination of whey protein with a DPP-Ⅳ inhibitor should also be examined, given the potential to augment the stimulation of GLP-1[121].

The timing of protein ingestion is important when aiming to stimulate incretin secretion and suppress appetite in advance of the main meal[48], and this, together with the optimal dose of whey protein, requires further refinement.

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