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Contents

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Xiu-Xia Song, Vice Director
World Journal of Diabetes
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
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PUBLISHER
Baishideng Publishing Group Inc
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Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
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REVIEW

Insulin-secreting β cells require a post-genomic concept

Fang-Xu Jiang, Grant Morahan

Fang-Xu Jiang, Islet Cell Development Program, Harry Perkins Institute of Medical Research, Nedlands, WA 6009, Australia

Grant Morahan, Centre for Diabetes Research, the University of Western Australia, Perth, WA 6009, Australia

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Correspondence to: Dr. Fang-Xu Jiang, Islet Cell Development Program, Harry Perkins Institute of Medical Research, 6 Verdun St, Nedlands, WA 6009,
Australia. fang-xu.jiang@perkins.uwa.edu.au
Telephone: +61-8-61510758
Fax: +61-8-61510701

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Abstract

Pancreatic insulin-secreting β cells are essential in maintaining normal glucose homeostasis accomplished by highly specialized transcription of insulin gene, of which occupies up to 40% their transcriptome. Deficiency of these cells causes diabetes mellitus, a global public health problem. Although tremendous endeavors have been made to generate insulin-secreting cells from human pluripotent stem cells (*i.e.*, primitive cells capable of giving rise to all cell types in the body), a regenerative therapy to diabetes has not yet been established. Furthermore, the nomenclature of β cells has become inconsistent, confusing and controversial due to the lack of standardized positive controls of developmental stage-matched *in vivo* cells. In order to minimize this negative impact and facilitate critical research in this field, a post-genomic concept of pancreatic β cells might be helpful. In this review article, we will briefly describe how β cells were discovered and islet lineage is developed that may help understand the cause of nomenclatural controversy, suggest a post-genomic definition and finally provide a conclusive remark on future research of this pivotal cell.

Key words: Beta cells; Insulin; Post-genome; Concept

Core tip: Pancreatic β cells are highly effective and efficient in the production of insulin, and specialized in its regulated secretion. Deficiency of β cells causes diabetes mellitus, the prevalence of which keeps climbing, despite new drugs continuously becoming available to clinics. Thus regenerative therapies to this devastating disease show great promise. Nevertheless, the generation of β cells requires multiple forced fate changes from pluripotent stem cells and the latter derived insulin+ cells expressing selective key β-cell transcription factors may not be the genuine islet counterparts. Hence their post-genomic concept may help the future development of diabetes regenerative therapies.

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INTRODUCTION

Pancreatic insulin-secreting β cells are of pivotal importance to our physiology because they play a central role in maintaining normal glucose homeostasis by their ability to produce and secrete insulin - a life hormone released in a fine-tuned manner as the body requires it. Deficiency of glucose-responsive β cells causes diabetes mellitus, a global public health issue with a progressively increasing prevalence. Absolute deficiency of these β cells due to autoimmune-mediated destruction results in type 1 diabetes mellitus (T1D). Relative deficiency leads to type 2 diabetes mellitus (T2D), caused by multiple issues, such as the failure of peripheral metabolic tissues to respond to insulin action, the liver's inability to control the production of glucose and the demise of islet β cells[1]. Diabetes mellitus currently affects over 387 million people worldwide. Despite a variety of treatments being continuously brought to the clinic, the incidence of this disorder is progressively climbing and is projected to reach 592 million by 2035[2]. Thus, there is an urgent need for novel treatments, such as regenerative medicine, a field established by the creation of human embryonic stem cells (ESCs) in 1998[3]. A regenerative therapy would provide a cure of T1D (should autoimmunity to β cells be controlled) and also for a subset of T2D, either by transplantation of donated hormone-secreting islets[4] or of *in vitro* generated genuine β cells from ESCs or induced pluripotent stem cells (iPSCs), or ultimately by regeneration *in situ* of endogenous β cells.

For diabetes regenerative medicine, tremendous focus has been applied to generate insulin-secreting β cells *in vitro*. However, over the years the nomenclature of β cells has unfortunately become inconsistent, confused and controversial, which in turn has apparently hampered the progress of the field. In order to minimize the negative impact of this confusion and to facilitate critical research, we suggest a post-genomic concept of pancreatic β cells. We will briefly describe how β cells were discovered and the islet lineage developed; how this controversy arose; suggest a post-genomic definition and finally provide concluding remarks on this vital research.

BRIEF HISTORICAL ACCOUNT

The "islet of Langerhans" was named after Paul Langerhans, a German medical student, who in 1869 observed small clusters of "clear cells" within the pancreas that were obviously different from the surrounding pancreatic tissue. Subsequently, Edouard Laguesse termed these clusters as islets of Langerhans (Figure 1). Approximately 30 years later, in 1907, Falkmer *et al*[5] found the islet cells harbored distinct granules that were different from the zymogen granules in the acinar cells. For example, one type of islet cells was basophilic (type B) stained by certain histochemical methods and another was not (type A). A more detailed description of how different types of endocrine cells in the pancreas may be distinguished is documented elsewhere.

In the year 1922, the B cells were discovered to produce the hormone insulin (Figure 1) by Banting and Best[6] who were awarded the Nobel prize for Medicine in 1923. The presence of insulin in the B cells (now known as β cells) was first confirmed immunohistochemically in 1957[7]. Glucagon was identified in the A cells (now known as α cells) in 1962; this hormone raises blood sugar levels by releasing glucose stored in the liver as glycogen, which is formed in a process called gluconeogenesis. Insulin was the first protein to be fully sequenced (*cf.* Figure 1). This was accomplished by Frederick Sanger's group in 1955[8] and in 1958 Sanger received the Nobel Prize in Chemistry for this hallmark discovery. In 1977, Ullrich *et al*[9] successfully cloned the insulin gene and its cDNA using recombinant DNA technology.

Since then, knowledge of this important cell type has increased exponentially. In particular following the creation of human ESCs, numerous academic groups and biotechnological companies have attempted to generate β cells *in vitro* from pluripotent stem cells (PSCs, which include ESCs and iPSCs) with the aim of advancing pancreas developmental biology, providing a renewable cell source for drug screening and, ultimately, establishing a regenerative therapy for diabetes. However, an associated negative effect of this period was the appearance of controversies and confusions on the definition of β cells. This confusion arose from simplistically treating PSC-derived insulin$^+$ cells expressing several markers of key β-cell transcription factors as a genuine counterpart of *in vivo* glucose-responding cells. In order to help understand this complex and controversial issue, we will briefly introduce the embryology of pancreas development.

EMBRYOLOGY

The pancreas is an endocrine as well as exocrine organ. It is derived from the primitive germ cell layer known as endoderm (the other two layers are the ectoderm and mesoderm) that originates from the inner cell mass from which ESCs were also originally derived. After gastrulation, the thickened endodermal epithelium along the dorsal and ventral surfaces of the posterior foregut gives rise to the primitive pancreas. In mice, this thickening can be identified histologically at embryonic day (E) 9.0-9.5[10].

The columnar epithelial cells expand into adjacent mesoderm-derived mesenchymal tissue and form the dorsal and ventral buds of the pancreas primordia. These expanding and branching buds fuse together as the developing gut rotates. The fused developing pancreas continues to grow, differentiate and, ultimately, develop into the mature organ. The adult pancreas consists of digestive fluid-transporting ductal tissue, digestive enzyme-secreting acinar tissue and hormone-secreting

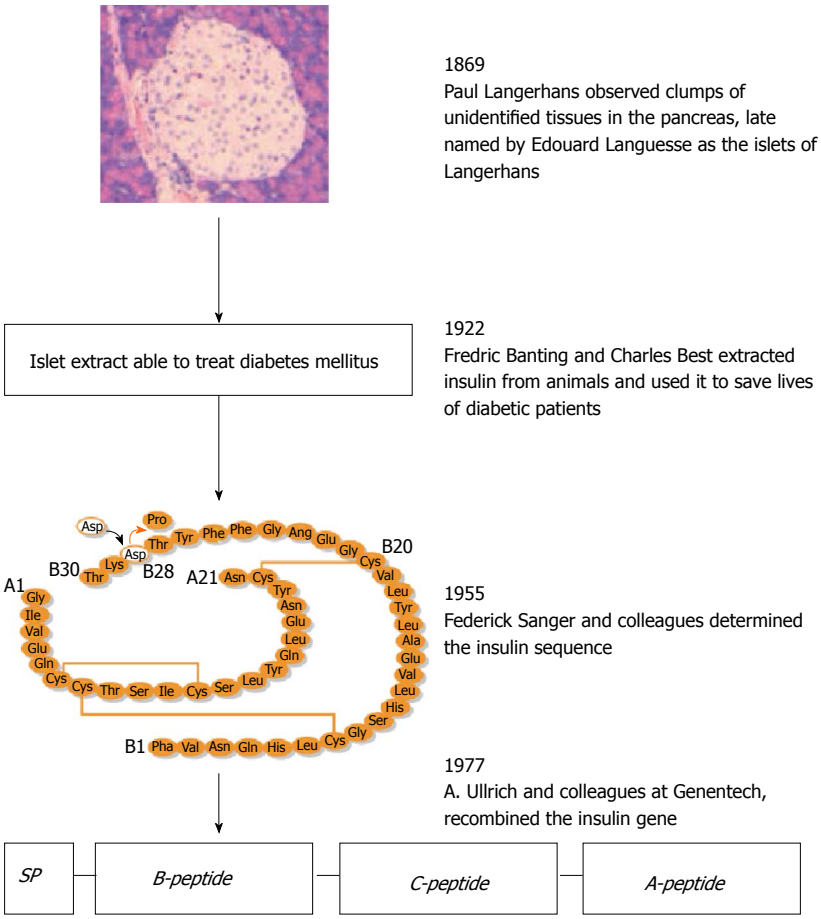

Figure 1 Historical account of the discovery of insulin. Presented four landmarked discoveries of the islets of Langerhans, insulin, the sequencing of insulin and insulin gene recombinant technology.

endocrine tissue located in the islets of Langerhans. The latter consist of five types of endocrine cells including in addition to the afore-mentioned β cells and α cells, somatostatin-secreting δ cells, pancreatic polypeptide-secreting PP cells and ghrelin-secreting ε cells.

Naturally, human pancreas development displays some features not observed in rodents. For example, the dorsal bud can be detected as early as 26 d post conception (dpc), an equivalent stage to E9.5 embryos in mice, but embryonic β cells are not visible until 52 dpc, approximately 2 wk later than the equivalent stage at which they could be detected in mice. The ontogeny of human embryonic β cells precedes that of embryonic α cells at 8-10 wk of development[11]. Genetic lineage tracing in mice demonstrates that embryonic β cells do not become postnatal functional insulin-secreting β cells[12]. All islet cells are detectable at the end of the first trimester in humans[11], but at very later stages (E17.5) in mice[13]. These data indicate that the sequence of key developmental events in human pancreatic development is distinct from that in mouse[14], and this is supported by differences in gene expression patterns during both developmental and disease processes in these species[15]. Further details of human pancreas development can be found in reviews elsewhere[16-20]. In the following sections, we will discuss several intermediate stages of islet development, in order to help understand how the confusing and controversial terminology concerning insulin-producing β cells appeared.

DEVELOPMENT OF INSULIN-SECRETING β CELLS

Definitive endoderm

One of three germ layers to appear during embryogenesis, the definitive endoderm gives rise to numerous organs in a process that is summarized in Figure 2. ESCs can be made *in vitro* to recapitulate their *in vivo* developmental pathways, to give rise to definitive endodermal (DE)-like cells by being cultured in the presence of a high concentration of activin A, a member of the transforming growth factor β superfamily. ESC-derived human expandable DE-like cells are termed endodermal progenitors[21]. Remarkably, they have been shown to self-renew in the presence of a group of growth factors comprised of bone morphogenetic protein 4, fibroblast growth factor 2, vascular endothelial growth factor and epidermal growth factor[21]. These progenitors can be passaged at least 24 times with a population expansion of five orders of magnitude. Furthermore, reprogrammed fibroblast-derived DE-like cells have been independently demonstrated to be capable of expanding approximately 65000-fold in the presence of activin A and LiCl[22]. These data suggest that these DE-like cells are highly proliferative. To ensure their correct

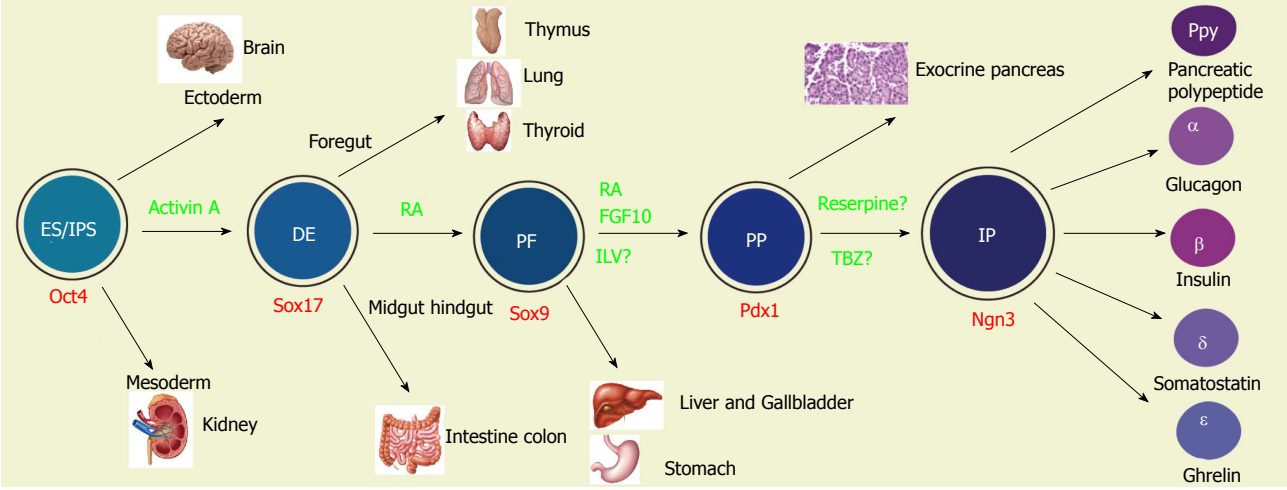

Figure 2 Multiple fate commitments of pluripotent stem cells lead to the development of insulin-secreting β cells. Whereas inner cell mass (ICM) gives rise to three germ layers (the ectoderm, mesoderm and endoderm) during gastrulation, embryonic stem cells (ESC) or induced pluripotent stem cells (iPSC) preferentially differentiate into definitive endodermal cells [DE, marked by the expression of Sox17 (the Sry-related HMG box transcription factor 17) and Foxa2 (foxhead homeobox 2a)] in the presence of activin A. Along the anterior-posterior axis the DE is divided into foregut (giving rise to the lung, thyroid and oesophagus), posterior foregut [PF, marked by the expression of the transcription factor Sox9 and hindgut (committing the intestine and colon)]. *In vitro*, retinoid acid would direct the DE cells to PF cells. Rather than to the stomach, liver and gallbladder, the PF cells preferentially give rise to pancreatic progenitors (PP, marked by the expression of the transcription factor Pdx1) in the presence of retinoid acid (RA) and fibroblast growth factor 10 (FGF10) or indolactam (ILV). Principally towards the exocrine and ductal tissues, the PP also commits to progenitors of the endocrine islet lineages [IP, marked by the expression of a high level of Ngn3, as well as NeuroD1 (neural differentiation 1), IA1 (insulinoma associated 1), Isl1 (Islet 1), Pax6 (paired box factor 6) and Rfx6]. The ES/iPSC-derived Pdx1+ cells gave rise to Ngn3$^+$ cells in the presence of tetrabenzine (TBZ). The IP then differentiates into five types of islet cells [α, β, δ (somatostatin), PP (pancreatic polypeptide) and ε (ghrelin)]. The "?" indicates that the differentiation factors have not yet been completely validated.

differentiation, the endodermal progenitors should be transcriptomically compared to isolated embryo derived DE cells, at least with mouse cells. Although further studies are required, these endodermal progenitors may provide expandable pre-pancreas progenitors for generation of insulin-secreting β cells.

Sox9-expressing progenitors

Sox genes transcribe members of the Sry (sex determining region Y) box-related high-mobility group transcription factor family and are versatile regulators of the stem/progenitor cell fate[23] as well as of embryonic development of many organs including the pancreas. Sox9 is a critical transcription factor detectable at E10.5 in the dorsal and ventral pancreatic epithelia[24]. Importantly, Sox9-expressing embryonic pancreatic epithelia at E13.5 have the capacity to give rise to acinar, ductal and islet lineages in the pancreas[25]. However, *Sox9* expression is gradually confined to pancreatic duct cells by E16.5[25]. Lineage tracing studies demonstrate that *Sox9* is also expressed in other posterior foregut-derived organs including the bile duct, the duodenum and the liver. For example, it is expressed in bile duct cells adjacent to the portal vein from E16.5. *Sox9* is also broadly expressed in the intestinal epithelia at E13.5 but become restricted to the crypt from E18.5[25]. These data indicate that PSC-derived Sox9-expressing cells may commit to multiple endoderm-derived lineages including the pancreas.

Pancreatic progenitors express Pdx1

A group of special cells in the thickened DE epithelium along the dorsal and ventral surfaces of the posterior mouse foregut at E9.0-9.5 expresses the gene named *Pdx1* (pancreas and duodenal homeobox 1, also known as *IPF1*, insulin promoter factor 1 in humans). Pdx1 is a transcription factor of the parahox homeobox family and is essential for both the expansion of pancreas primordial populations[26] and the function of adult β cells[27,28]. Genetic lineage tracing experiments demonstrated that pancreatic Pdx1-expressing (Pdx1$^+$) progenitors give rise to acinar, duct and endocrine tissues in the pancreas[29]. These progenitors are located at the tip of the branching pancreatic tree marked by Pdx1$^+$Ptf1a$^+$ (pancreas transcription factor 1a) Cpa1$^+$(carboxypeptidase 1)[30]. Replacement of most of the homeodomain of PDX-1 with the lacZ reporter, allows visualization of the PDX-1/β-galactosidase fusion allele, and it was found to be expressed in pancreatic, duodenal and antral stomach lineages[31]. The non-pancreas endoderm-derived expression of Pdx1 was established with the application of a different labeling strategy[32]. These studies suggest that PSC-derived Pdx1$^+$ cells may commit to any of these lineages. Thus, caution should be taken because all PSC-derived Pdx1$^+$ cells may not be the equivalent of the pancreatic Pdx1$^+$ progenitors.

In humans, numerous PDX1$^+$ progenitors can be detected easily in the developing pancreas between 8 and 21 wk of age[33,34]. These PDX1$^+$ progenitors frequently express SOX9 and are highly proliferative[35], supporting the notion that PDX1$^+$ progenitors are committed from SOX9$^+$ multipotent progenitors. The number of PDX1$^+$ cells that also express insulin or somatostatin progressively increases during this period of development[33]. An unanswered fundamental question is the origin of the PDX1$^+$

progenitors: Are they generated by self-renewal, or by commitment from their endodermal progenitors, or from both sources?

Following *in vivo* developmental pathways, PSCs can be directed to give rise to Pdx1$^+$ cells in the presence of the protein kinase C activator indolactam (ILV)[36]. These cells are able to proliferate 16-fold in the presence of pancreas-derived mesenchymal cells[37]. Independent confirmation of these results is essential to verify this capacity of the Pdx1$^+$ cells. It is also important to address whether all or only a minor fraction of PSC-derived Pdx1$^+$ cells commit along the endocrine pathway. To resolve these issues, identification of a specific marker that allows the purification of the Pdx1$^+$ pancreatic progenitor-like cells would be valuable.

Ngn3-expressing islet progenitors

At around E9.5 in mice, a small group of cells in the thickened posterior foregut DE epithelium begins to express the basic helix-loop-helix transcription factor neurogenin 3 (Ngn3, also known as neurog3)[29,38,39]. These Ngn3$^+$ cells are islet progenitors because they can give rise to all islet lineage cells. Whereas mouse *Ngn3* mRNA expression in the developing pancreas peaks around E15.5[40] (equivalent to week 9 in humans), human *NGN3* expression is low before 9 wk, from which time, its expression increases sharply and remains high until 17 wk[34].

A number of observations support the importance of Ngn3 in islet development: Islet cells are not observed in *Ngn3* knockout mice[38]; gene lineage tracing demonstrates that Ngn3$^+$ progenitors give rise to all pancreatic endocrine cells[29]; in adult pancreas, purified Ngn3$^+$ cells activated by pancreatic duct ligation (PDL) can, after injection into a fetal pancreas *in vitro*, differentiate into all islet cell types[39]. In contrast, one group reported that although PDL allows activation of Ngn3 expression, the Ngn3$^+$ cells were not able to complete the entire β-cell developmental program[41] and a more recent study found that β-cell mass and insulin content were totally unchanged by PDL-induced injury[42]. The reason for these inconsistencies is unknown so future studies are required to resolve this matter.

Interestingly, insulin protein has been detected in islet progenitors in the developing human and mouse pancreas. In a dual fluorescence reporter mouse line, a few Ngn3$^+$ cells in the developing pancreas coexpress insulin[43]. In humans, some NGN3$^+$ cells were also detected to coexpress insulin in the fetal pancreas between 10 and 21 wk[33]. Recently, inhibitors of vesicular monoamine transporter-2 (reserpine and tetrabenzine, TBZ), were shown to mediate differentiation of PSC-derived Pdx1$^+$ cells into *Ngn3*-expressing cells[44]. Again, caution has to be taken regarding the use of genetic lineage tracing in PSC differentiation because successful *in vivo* lineage tracing studies rely on the temporospatial cues (see review[45]) and Ngn3-expressing cells are present in multiple tissues including the endoderm-derived intestine[46]. Despite lineage tracing demonstrating that Ngn3$^+$ cells will complete the differentiation process prenatally to all pancreatic endocrine cells including β cells[29], these only become glucose-responsive postnatally.

INSULIN-SECRETING β CELLS

In adults, there are approximately 1000 endocrine islets in mice and 1 × 10^6 in humans distributed throughout a healthy pancreas, representing up to 2% of the total mass of the organ[47]. Each islet varies in size from 100 to 500 μm in diameter and is made up of 1000-3000 cells[48]. In rodents, β cells are the major component, accounting for up to 80% of the total number in the islets, with the remainder comprised of α cells (approximately 15%) and the remaining endocrine δ, PP and ε cells (approximately 5%). In the human islet, the proportions of δ and PP cells are similar, but β cells are less abundant (48%-59%) and the α-cell population accounts a 33%-46%[49]. Interestingly, a substantial number of ε cells are found in adult islets in humans, but not in other known species[50].

Insulin orchestrates blood glucose utilization by peripheral metabolic tissues such as the liver, muscle and adipose tissue, while glucagon raises blood glucose concentrations by acting on the liver, brain, adipose tissue and heart[51]. Thus both hormones are critical in maintaining glucose homeostasis. A close paracrine regulatory loop is present between α and β cells. For example, β cells secrete urocortin 3 to stimulate the release of somatostatin which in turn suppresses secreting glucagon from α cells[52]; α cells also generate ghrelin, which is normally believed to be produced by ε cells, to inhibit insulin secretion but stimulate their own glucagon secretion[53].

Clearly, the β cell is a highly effective and efficient factory specialized for the production of insulin. For example, on average a rodent β cell contains approximately 10000 insulin granules (Figure 3), corresponding to approximately 10%-20% of the total cell volume. Each granule stores approximately 2 × 10^5 insulin molecules, thus a β cell could package 2 × 10^9 insulin molecules[48]. At least 17 key transcription factors (including FOXA2, FOXO1, HNF1A, INSM1, ISL1, MAFA, MNX1, MYT1, NEUROD1, NKX2.2, NKX6.1, PAX6, PDX1, RFX6 TCF7L2 and RFX3) are required to maintain β-cell function[54]; some of these are shown in Figure 3. The basic-leucine zipper transcription factor MAFA (musculoaponeurotic fibrosarcoma oncogene family protein A), for example, is an important *INS* transactivator[55]. PDX1 is well known to activate and maintain *INS* and *GLUT2* (glucose transporter 2) expression in β cells[56,57]. A gene network controlled by NKX6.1 is essential for maintaining the functional and molecular traits of mature β cells[58]. Pancreatic β cells require NEUROD1 (neuronal differentiation 1) to achieve and maintain a functional state[59] by DNA methylation-mediated repression of the lineage determination gene aristaless-related homeobox[60]. In addition to key transcription factors, the fractalkine (also known as CXCL1 or neurotoxin)/CXCL1R (also known as GPR13) system

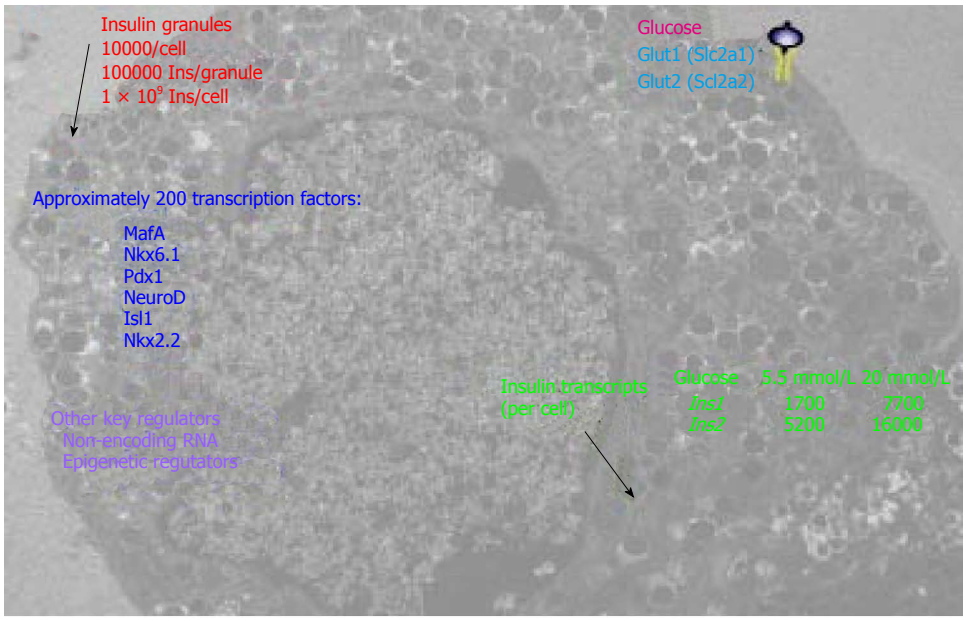

Figure 3 An integral view of insulin-secreting β cells. The highly specialized cells have a powerful function that is regulated by multiple layers of signaling.

also regulates β-cell function and insulin secretion[61]. Furthermore, β cells develop a highly sophisticated electrophysiology[62] and glucose sensing system for blood glucose concentrations for fine-tuned secretion of insulin granules to maintain normal glucose homeostasis, which is critical for normal physiology of many pivotal organs.

Recently, the application of high throughput RNA and DNA sequencing technologies has given us a more integral view of insulin-secreting β cells. Deep RNA sequencing of purified human β cells demonstrated *INS* is the most abundantly transcribed gene, representing approximately 38% of the β-cell transcriptome[63], within which also contains transcripts from over 9900 other genes[64]. Massively parallel signature sequencing demonstrated that there are over 200 β-cell specific transcription factor genes[65] that regulate this fine-tuned function. Uniquely, the human *INS* gene is marked by high levels of histone acetylation and H3K4 demethylation at around approximately 80 kb from the transcription start site. These modifications in many other human genes are concentrated around only 1 kb of the start site[66]. Consistently, high-throughput sequencing of formaldehyde-assisted isolation of regulatory elements (FAIRE-seq) identified approximately 3300 human islet-selective open chromatin sites[67]. Polyadenylated mRNA sequencing reveals that over 1000 long intergenic noncoding RNA species are transcribed in mouse and human β cells[68,69]. A review of transcriptomes and other omics of β cells can be found elsewhere[70].

CONFUSION IN THE CONCEPT OF β CELLS

Reductionist approaches applied over the last two decades have uncovered a complex transcription regulatory network for islet lineage development[71,72]. Despite the fact that intense international efforts have concentrated on differentiation of PSCs for replacing/restoring the lost β cell function, application of this knowledge for translational research to produce functional β cells *in vitro* has not been straightforward. This is because knowledge generated from *in vivo* studies in rodent models is not necessarily applicable to *in vitro* studies, in particular for human cells. Over this period, at least 11 nomenclatures and definitions have been given to insulin-producing cells (Figure 4) that were generally believed to be the equivalent of *in vivo* β cells.

As the pancreatic islet population and neural cells share a large number of markers and perhaps mechanisms of differentiation[73], mouse ESCs were early reported to give rise to insulin-positive cells in culture conditions that were used for neural cell differentiation[74]. Although the differentiated cells were stained positive for insulin, it was subsequently shown this was due to the uptake of insulin from the culture medium rather than the activation of robust insulin transcription[75]. Additionally, there were several reports of generating pancreatic endocrine cells or functional β cells from PSCs[76-78]. Later these cells were however demonstrated to be similar to fetal β cells[79] and to lack the transcriptomic and epigenetic profiles of adult islet cells[80].

Nevertheless in such a short timeframe, PSCs have been convincingly differentiated following their normal *in vivo* developmental mechanisms into cells of approximately at the pancreatic progenitor and/or islet progenitor stages[21,36,37,80-84]. In contrast, due to a lack of knowledge of the late stage pancreatic endocrine lineage[85,86], empirical protocols have been used for their further differentiation. Inevitably the PSC-derived endocrine populations may only contain a small fraction of genuine insulin-secreting cells or are immature, as reversal of diabetes in mice requires

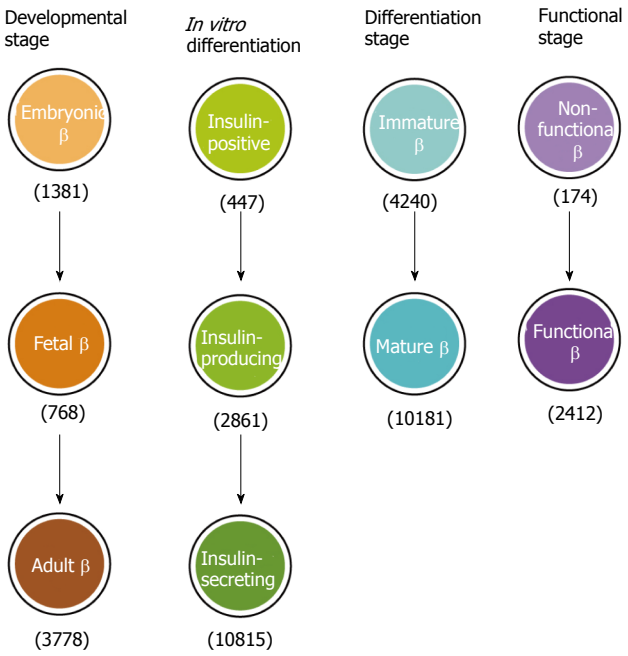

Figure 4 Conceptual confusions in insulin-secreting β cells. Insulin-secreting cells have been given a variety of nomenclature depending on the developmental stages, *in vitro* differentiation, functional states or reprogram/transdifferentiation. The number of used nomenclature in parenthesis was from a Pubmed search in May 2015.

five million SC-β cells[87] or further maturation *in vivo*[88]. Readers are referred to recent fine reviews regarding the current state and problems on PSC differentiation towards pancreatic endocrine cells[20,86,89-91]. Perhaps the problems and confusions on the concept of insulin-secreting β cells seem to have produced negative impacts in the academic community while generating unhelpful excitement and expectations on the reality of future diabetes regenerative medicine to the general public. Furthermore, the confusion and controversy has hampered the progress of not only the field of islet developmental biology but also the establishment of a regenerative therapy to diabetes *per se*. The following section exemplifies several potential, but not exclusive, causes of the confusion and controversy.

The presence of extrapancreas insulin-producing cells

Making the issues more complicated, multiple sites in the body can produce insulin. The thymus, another foregut-derived organ (Figure 2), for example, normally produces insulin, in order to induce self-tolerance and protection of the body from the autoimmune destruction of pancreatic insulin-secreting β cells[92] as thymus-specific deletion of insulin results in both autoimmune destruction of these cells and diabetes[93]. Certain areas of the brain also express the insulin gene and produce insulin protein[94] and these share several transcription factors of the islet lineage[73]. In different diabetic models, including streptozotocin-treated mice and rats, ob/ob mice, and mice fed high-fat diets, insulin mRNA and protein expression have been detected in the liver, adipose tissue, spleen, bone marrow as well as thymus[95]. An interesting question is whether these extrapancreatic insulin-producing cells are able to give rise *in vitro* to functional insulin-secreting cells. Otherwise, such extrapancreatic insulin-producing cells are simply non-functional cells. Taken together, these data suggest that PSC-derived insulin-producing cells might consist of physiologically irrelevant insulin-producing cells.

Multiple fate commitments may accumulate non-functional insulin-producing cells

PSCs theoretically have the capacity to give rise to all of the functionally-defined 210 cell types in the body, so to induce them to becoming desirable β cells requires forcing them to make multiple fate commitments under the guidance of exogenous differentiation factors (Figure 2). Treatment with these factors of course is not always 100% effective, resulting in some cells differentiating along unwanted pathways, even giving rise to non-functional insulin-producing cells especially in suboptimal or abnormal differentiation conditions. Currently, there is no documentation on whether any PSC-derived insulin-producing cells in the differentiated product are similar to those of extrapancreas-derived ones.

Empirical protocol may generate non-functional insulin-producing cells

The lack of knowledge of differentiation of late stage islet lineages[85,86] led researchers to develop cocktail protocols containing factors that have not been well-characterized. Development of such protocols depends heavily on the experience of researchers and poorly characterized combinations of factors may promote generation of non-functional insulin-producing cells. A better understanding of the β-cell differentiation pathway and its underlying mechanisms would therefore allow the establishment of a standardized directed differentiation protocol and stage-specific differentiation strategies, so that generation of non-functional insulin-producing cells could be minimized or avoided.

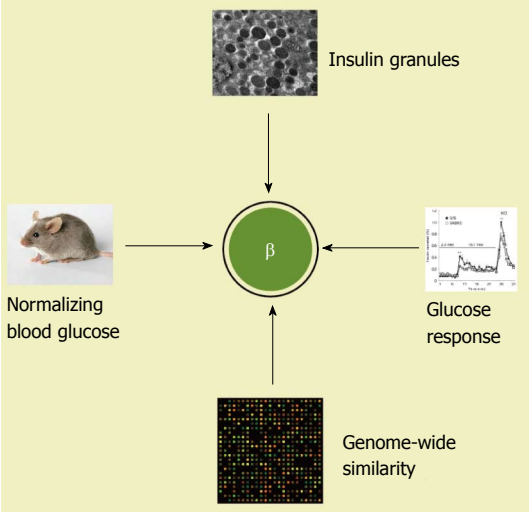

Figure 5 A post-genomic concept of insulin-secreting β cells. Whereas four criteria are proposed, a highly similar transcriptomic profile to adult β cells is essential to establish pluripotent stem cells-derived β cells.

β CELLS REQUIRE A POST-GENOMIC CONCEPT

A major obstacle/challenge in defining PSC-derived insulin-secreting β cells is that the temporospatial cues that help identify these *in vivo* are absent in differentiation *in vitro*. As insulin is only a member of an insulin-related family[96,97], it is critical to absolutely exclude whether any of the insulin antibodies (especially polyclonals) that have been used to characterize "insulin-producing cells" do not cross-react with other members of this family or even with other polypeptides. This is because "antibodies often recognize extra proteins in addition to the ones they are told to detect" and their reproducibility needs to be dramatically improved[98,99].

We propose at least four essential criteria for insulin-secreting β cells for further discussions and considerations. Compared to adult β cells, the *in vitro* PSC-derived cells must have: (1) An equivalent number of insulin granules under electron microscopy; (2) a similar dynamic glucose stimulated insulin secretion; (3) a highly similar transcriptomic profile (not a similarity in a selected gene profile of transcriptomic datasets), and (4) the capability to normalize hyperglycemia within a few weeks after transplantation as an equivalent number of functional β cells do (Figure 5).

Definition of functional insulin-secreting β cells at the transcriptomic level is an essential requirement. Alternatively, single-cell transcriptomic and epigenomic analyses of PSC-derived insulin-producing cells could help establish this concept.

CONCLUSION

Currently the sophisticated insulin pump also known as the "Closed Loop Therapy" or "Artificial Pancreas" can deliver insulin in a precise manner, resulting in a significant improvement in the blood glucose control and the quality of life for people with diabetes[100,101]. Perhaps we should exercise extra caution for stem cell therapies to diabetes, due to the concern of tumorogenesis[102], off-target differentiation[89], biosafety and reliability having not yet been convincingly addressed. The application of genomic, epigenomic, transcriptomic, and/or proteomic approaches to characterize differentiated products will not only verify their safety profile and differentiated state but also shed light on their transcription regulation and molecular mechanisms. The pharmaceutical and biotechnological sectors should work together with the academic community to strengthen fundamental research, identify ways to purify/enrich PSC-derived progenitors at specific stages and develop directed differentiation protocols for the development of the stage-specific progenitors towards genuine insulin-secreting β cells. The progenitors at different stages and differentiated insulin-secreting cells would also be useful for fundamental research and drug screening. Thus, the ability to generate the highly specialized functional β cells *in vitro* will not only generate new knowledge of pancreatic endocrine lineages, but also provide a critical cell source for a diabetes regenerative therapy, a potentially robust and better medicine. In doing so, safe, stable, reliable and functional cellular products will ultimately be available to people with T1D and those with some forms of T2D.

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Evidence based review of type 2 diabetes prevention and management in low and middle income countries

Aimee Afable, Nidhi Shree Karingula

Aimee Afable, Nidhi Shree Karingula, Department of Community Health Sciences, SUNY Downstate School of Public Health, New York, NY 11203, United States

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Correspondence to: Aimee Afable, PhD, MPH, Assistant Professor, Department of Community Health Sciences, SUNY Downstate School of Public Health, 450 Clarkson Avenue, Box 43, Brooklyn, New York, NY 11203, United States. aimee.afable-munsuz@downstate.edu
Telephone: +1-718-2706397
Fax: +1-718-2215157

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Abstract

AIM: To identify the newest approaches to type 2 diabetes (T2DM) prevention and control in the developing world context.

METHODS: We conducted a systematic review of published studies of diabetes prevention and control programs in low and middle-income countries, as defined by the World Bank. We searched PubMed using Medical Subject Headings terms. Studies needed to satisfy four criteria: (1) Must be experimental; (2) Must include patients with T2DM or focusing on prevention of T2DM; (3) Must have a lifestyle intervention component; (4) Must be written in English; and (5) Must have measurable outcomes related to diabetes.

RESULTS: A total of 66 studies from 20 developing countries were gathered with publication dates through September 2014. India contributed the largest number of trials (11/66). Of the total 66 studies reviewed, all but 3 studies reported evidence of favorable outcomes in the prevention and control of type 2 diabetes. The overwhelming majority of studies reported on diabetes management (56/66), and among these more than half were structured lifestyle education programs. The evidence suggests that lifestyle education led by allied health professionals (nurses, pharmacists) were as effective as those led by physicians or a team of clinicians. The remaining diabetes management interventions focused on diet or exercise, but the evidence to recommend one approach over another was weak.

CONCLUSION: Large experimental diabetes prevention/control studies of dietary and exercise interventions are lacking particularly those that consider quality rather than quantity of carbohydrates and alternative exercise.

Key words: Diabetes prevention and control; Low-income countries; Middle-income countries; Intervention research; Systematic reviews

Core tip: We conducted a systematic review of published

efficacy studies of diabetes prevention and control programs in low and middle-income countries. A total of 66 studies from 20 countries were gathered, based on our selection criteria. Of the 66 studies, all but 3 reported evidence of efficacy. Structured lifestyle education programs were the most common strategies. There was also a diverse range of dietary and exercise approaches. However, large experimental studies of their efficacy, particularly with regard to studies comparing alternative exercise to aerobic and quality of carbohydrates to quantity, are lacking.

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INTRODUCTION

Diabetes leads to both premature death and complications such as blindness, amputations, renal disease, and cardiovascular diseases[1]. It is well known that risk factors for diabetes such as physical activity and diet are modifiable and can possibly be reversed with adjustments in lifestyle; there is an opportunity to intervene and prevent or delay onset of diabetes.

Diabetes often disproportionately affects low- and middle-income countries. More than 382 million people (8.3%) in this world are suffering from diabetes and it is projected to rise to more than 592 million by 2035[2]. China and India lead in the number of cases worldwide. For example, it is estimated that 98.4 million adults in China and 65.1 million in India have diabetes[2]. China now has the largest epidemic worldwide and recent study suggest that diabetes prevalence in China has surpassed the United States with 11.6% of Chinese adults having diabetes[3].

Diabetes growth worldwide has been attributed to global secular shifts in lifestyles that result from upward social mobility and rapid urbanization[4-8]. Intra-country migrants who move from rural to urban areas, or who transition from poverty to affluence, for example, can take on more sedentary jobs, markedly different from their former labor-intensive work and adopt less healthy diets[9,10]. This shift to a more sedentary lifestyle and greater consumption of processed foods and total energy intake is common in middle-income countries undergoing rapid urbanization, a process that has been labeled the "nutrition transition"[11,12].

Further, diabetes is now affecting younger and middle-aged adults who are at the peak of their economic productivity[13-16]. Costs associated with the care and management of diabetes worldwide is significant. People with diabetes have more outpatient visits, use more medications, have a higher probability of being hospitalized, and are more likely to require emergency and long-term care than people without the disease[17,18]. In the United States for example, chronic disease management and diabetes in particular is a major driver of healthcare costs[19]. In the United States, people with diabetes have 2-3 times health care costs compared to those without diabetes[18]. According to American Diabetes Association, total costs of diagnosed diabetes have risen to $245 billion in 2012 from $174 billion in 2007. United States adults with diagnosed diabetes incur average medical expenditures of about $13700 per year, of which about $7900 is attributed to diabetes[18].

Research on the efficacy of diabetes prevention and control efforts have been concentrated in the United States and Europe[15,20,21], but the burden of disease is felt around the globe. By limiting research to high-income countries we may neglect the potential for high- and low-income countries to learn from each other, and for leveraging global resources in the development of more cost-effective strategies[14]. The National Institutes of Health-funded randomized controlled trial in the United States, the Diabetes Prevention Program (DPP), reported a 58% reduction in risk of developing type 2 diabetes through intensive lifestyle intervention among participants who were overweight and had prediabetes[22]. United States and global efforts are underway to translate this trial to populations who are disproportionately affected[20,21]. A meta-analysis of DPP translations in the United States highlights significant heterogeneity in approaches to translation including the use of allied health professionals *vs* lay community members to deliver lifestyle education; with regard to the number of educational sessions and the integration of technology[20]. Overall, Ali *et al*[20] found an adjusted pooled mean weight loss of 4 pounds. The authors conclude that there was no consistent pattern with regard to which type of DPP translation was more effective. However, they argued that there was no evidence to suggest that interventions that used lay members as opposed to allied health professionals were less effective; they propose that the use of lay health members to deliver lifestyle education are potentially more cost-effective than those that use allied health professionals.

Building on the Ali *et al*[20] review, this paper aims to identify the newest approaches to diabetes prevention and control in the developing world context, and highlight the unique considerations and challenges when working to prevent and manage chronic disease from a global perspective. The specific objectives of our review are the following (1) to evaluate whether interventions that are similar to DPP in the developing world are effective; (2) identify interventions that are substantively different from the DPP (with regard to intervention components); and (3) among this latter group, evaluate whether there is evidence of efficacy.

MATERIALS AND METHODS

According to the World Bank New Country Classifications, low and middle income countries are considered developing economies[23]. A low income country is defined as having

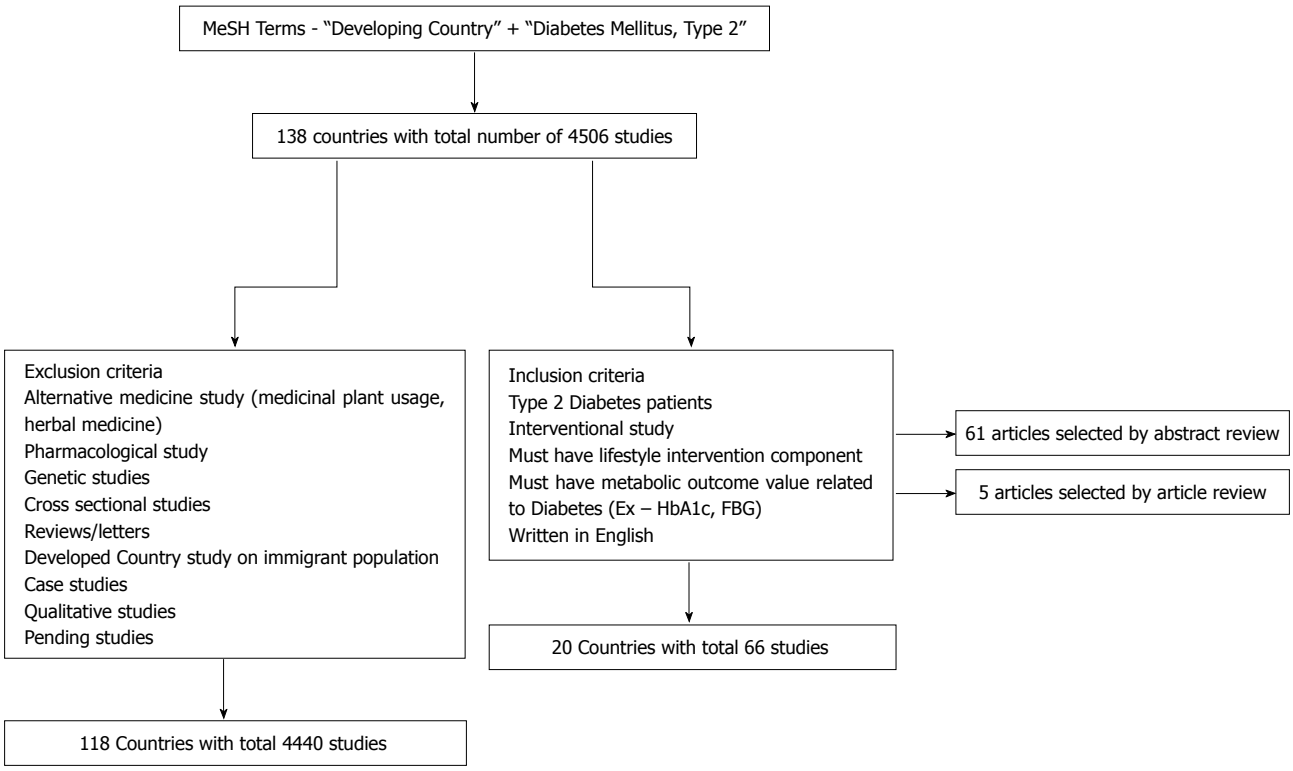

Figure 1 Systematic search methodology and results.

a gross national income (GNI) of $1035 or less, whereas a middle income country is defined as having a GNI between $1036 and $12615[1]. Currently, 138 countries in the world are considered to be developing economies. Using this list of countries, a systematic search through PubMed was conducted. Using Medical Subject Headings (MeSH terms), studies in the developing world on type 2 diabetes (T2DM) were obtained. For example, to search through studies in Algeria, the following terms were used - "Diabetes Mellitus, Type 2"(Mesh) AND "Algeria"(Mesh). Thus, searching country by country, 4506 studies involving type 2 diabetes were gathered from 97 developing countries during two search phases: September 2013 to December 2013 and an updated search during August 2014 to September 2014.

These studies were subsequently manually sorted using a pre-determined inclusion and exclusion criteria. The study needed to satisfy four criteria: (1) Must be experimental; (2) Must include patients with T2DM or focusing on prevention of T2DM; (3) Must have a lifestyle intervention component; (4) Must be written in English; and (5) Must have measurable outcomes related to diabetes. Specifically, "Lifestyle Intervention" was defined as any intervention that involved an exercise, dietary, behavioral change element modification. The behavioral change also included counseling on self-management, smoking cessation or stress management. Additionally, a measurable outcome value was defined as any outcome measure of diabetes or risk factor for diabetes such as hemoglobin A1c (HbA1c), fasting plasma glucose, blood glucose and insulin levels, and body mass index/obesity.

Using the above mentioned inclusion criteria, the studies were manually reviewed and filtered. Studies were excluded if they were: (1) Non-experimental/observational; (2) Pharmacological Studies; (3) Reviews; (4) Evaluated herbal medicines only; (5) Genetic Studies (studies that looked at specific gene variations in diabetic patients); (6) Studies that were conducted on immigrant populations in developed countries; and (7) Pending Studies. Based on the inclusion criteria, the studies were first filtered through abstract review and article review. Sixty-one articles were selected by abstract review and 5 articles were selected from article review. Therefore, a total of 66 studies from 20 developing countries were gathered after applying these inclusion and 4450 studies from 119 countries were excluded based on the exclusion criteria. Six pending studies were also collected and separately recorded. Figure 1 gives a visual reference of the search methodology.

Finally to address the primary objectives of the review paper, studies were classified into three categories: (1) Those most similar to the DPP and thus had a primary emphasis on lifestyle education/counseling delivered by allied health professionals or lay members of the community where dietary and exercise modification were recommended but not provided; (2) Intervention studies where structured dietary plans and exercise/activity modification were the main components; and (3) Any intervention that integrated some form of technology (texting, website, telephone, glucose monitor, *etc.*). We assess evidence of efficacy[24]. We defined a study as having evidence of efficacy if there were statistically significant differences: (1) Between baseline and follow-up

in experimental group; or (2) Between experimental and control groups in any of the primary outcomes reported.

RESULTS

Diabetes management: *DPP adaptations*

As shown in Table 1 nature of the intervention and study methodology varied widely among the studies reviewed. For example, among the 29 interventions that were most similar to DPP that were evaluated, 15 were randomized control trials (RCTs) and the remainder utilized quasi-experimental designs to evaluate the efficacy of the interventions. Sample size also varied in this group of studies. For example, the Turkish RCT by Mollaoğlu *et al*[25] 2009 had a sample size of 50; in contrast the RCT conduct in Bulgaria by Tankova, 2004 had a sample size of 560[26]. Among all study countries, Brazil and Thailand contributed the largest number of trials (5 and 4 respectively).

Among all 29 interventions, the follow-up period for outcome measurement also varied with a minimum of 2 mo follow-up[25] to a maximum follow-up period of 7 years[27]. Of all 29 studies, the Iranian study (Sarrafzadegan *et al*[27], 2013) was quite impressive. They evaluated the impact of a community-based lifestyle education mass-media intervention in a population of 9032 adults and during a follow-up period of 7 years and found significant declines abdominal obesity, hypertension and lipid biomarkers; however, there were not significant changes in blood glucose and diabetes prevalence[27].

Of the 29 interventions, all but 2 studies found significant improvements in diabetes related outcomes. Eight interventions delivered intensive lifestyle modification sessions by a physician or team of clinicians (*e.g.*, nutritionist, nurse, physician) and all but 1 study[28] found significant improvements in glycemic control in the experimental groups[26,29-34]. Twelve of the interventions were nurse-led, and all but 1 study[25] found significant improvement in glycemic control and/or significant decline in body mass index (BMI)[33,35-44]. Eight of the interventions were pharmacist-led and focused primarily on medication consultation (adherence and adjustments in dosage) and in some cases also included lifestyle education; all found significant improvement in glycemic control in experimental group[45-52]. Only one of the studies (in Jamaica) utilized lay health workers to deliver lifestyle education, and found significant decline in HbA1c levels in the experimental group[53].

Diabetes management: *Diet and exercise as main component*

As shown in Table 2, India contributed the largest number of trials with 6 total. Among all 18 studies, the nature of the intervention and study methodology varied widely. All 18 studies found significant improvements in diabetes related outcomes. Study designs varied and length of follow-up ranged from 2 wk (Chaiopanont[54], 2008) to 3 years (Oli *et al*[55], 1984). Among the 18 interventions, 7 focused exclusively on modifying diet with an emphasis on increasing fiber intake, introduction of low glycemic foods or variation in carbohydrate content[55-60]; these interventions took place in Brazil, India, Nigeria, Thailand and Mexico. It is notable that all of these studies were pilot studies with very small sample sizes ranging from 10 (Komindr *et al*[58], 2001) to 160 (Oli *et al*[55], 1984). In all the studies that used single group designs, all reported significant improvements in blood glucose control or cardiovascular risk factors. Oli *et al*[55], one of the largest trials, investigated the noteworthy question of whether diabetic patients can maintain blood glucose control with a high carbohydrate diet, consisting of readily available Nigerian foods and found excellent/good blood glucose control in over half of their patients (mean fasting blood glucose of 7-8 mmol/L or less). In the only study that used an RCT crossover design in Mexico (n = 14), there was HbA1c was significantly lower during the low-glycemic index period relative to the high-glycemic index period[59]. In addition one small Indian cross-over study examined the effect of camel milk on glycemic control and insulin sensitivity and found lower HbA1c in the diabetic group that drank camel milk (and deterioration in glycemic control when they drank cow milk)[61].

Ten of the 18 studies focused exclusively on a structured physical activity program. These studies investigated the efficacy of some form of structured exercise including aerobic walking/exercise (in some cases these studies also involved nutrition counseling but no structured diet)[62-66], progressive resistance training (PRT)[67,68], mixed aerobic/PRT exercise program[69]; and yoga/breathing/sitting/relaxation program[54,70]. All 10 studies found improvements in blood glucose control[54,63-69], BMI[70] or general well-being[62]. Among these 10, 4 were RCTs[62-64,68]. It is notable that the RCT conducted by Arora *et al*[68], 2009 in India found significant decreases in HbA1c levels in PRT group, which was comparable to the decrease in HbA1c level in the aerobic exercise group. Similarly, the largest trial of the structured exercise studies, which was conducted in South Africa, found significant decreases in HbA1c levels in both relaxation group and its comparison the aerobic exercise group[63]. Only 1 study in China involved both structured exercise and dietary change components; this was an RCT and found significant improvements in glycemic control in experimental group[71].

Diabetes management: Technology assisted interventions

In total we identified 9 interventions that integrated some form of technology including glucose monitoring systems, telehealth, multi-media and short message service (SMS) texting (Table 3). Three studies from Bangladesh, Bulgaria, and Malaysia evaluated the efficacy of home/self-monitoring of glucose (and also integrated health/lifestyle education); all three found significant improvements in glycemic control[72-74]. It is notable that both Kempf *et al*[73] and Ismail *et al*[74]

Table 1 Diabetes management: Diabetes Prevention Program like interventions (allied health professionals and lay member facilitated)

Country	Ref.	Objective	Study design	Sample size/ characteristics	Components of intervention	Measurements	Outcome measures	Conclusion
Argentina	Gagliardino *et al*[29]	To evaluate effect of combined physician and/or patient education and effect of system interventions (100% coverage of medications, formalized data collection)	Randomized 2 × 2 design trial	*n* = 468, 117 in control group (g1), 117 in physician education group (g2), 117 in patient education group (g3), 117 in physician and patient education group (g4), T2DM for at least 2 yr, age b/w25 and 75 yr	For T2DM pts - 90-120 min weekly teaching units For physicians - 25 structured module interactive course	HbA1c, BMI, FBG	0, 6, 12, 18, 24, 30, 36, 42 mo	HbA1c decreased from 4 mmol/mol to 10 mmol/mol (P < 0.05), with the largest decrease being in g4 (physician and patient education group)
Brazil	Cezaretto *et al*[30]	To evaluate effect of interdisciplinary intervention program	Two group randomized longitudinal	*n* = 135, 60 in traditional group, 75 in intensive group, high risk individuals for T2DM between ages 18 and 79	Intensive Intervention group - 2 h group sessions from 4 sessions in month 1 to 2 sessions in month 2 and 1 monthly sessions until 9 mo, print materials, telephone calls, interdisciplinary team included endocrinologist, psychologist, nutritionist, and physical educator	FBS, BMI, post load plasma glucose	0 and 9 mo	Intensive intervention group decreased fasting plasma glucose from 98.9 to 95.3 (P < 0.001), while the traditional intervention group was not significant. Intensive intervention group BMI decreased from 31.7 to 30.9 (P < 0.001) while the traditional intervention group BMI decreased from 29.9 to 29.1 (P < 0.001)
Brazil	Chaves-Fonseca *et al*[31]	To evaluate effectiveness of "staged diabetes management" protocol	RCT	*n* = 113, 47 in control group, 66 in intervention group > 30 yr old, T2DM	SDM protocol (as developed International diabetes center) with doctor, nurse, pharmacist and health technicians	HbA1c, random glucose	0, 12 and 18 mo	Random glucose decreased from 12.7 to 10.5 (P = 0.004) and HbA1c decreased from 9.2 to 7.7 (P < 0.001) in intervention group, while there was no significant change in intervention group
Brazil	Mourão *et al*[49]	To evaluate effectiveness of pharmaceutical care program	RCT	*n* = 100, 50 in control and interventional, > 18 yr, HbA1c > 7%, post prandial capillary glucose > 180 mg/dL, T2DM	Two research pharmacists conducted education on drug therapy problems, medication adherence	HbA1c, fasting blood glucose	0 and 6 mo	HbA1c decreased -0.6% and fasting blood glucose decreased -21.4 mg/dL in intervention group (P = 0.001)
Brazil	Correr *et al*[50]	To evaluate effect of pharmacotherapy follow up	RCT	*n* = 96, 50 in intervention and 46 in control, > 30 yr old, diagnosed T2DM, oral meds or insulin use	Monthly visit with pharmacist for education, suggestion in changes of medication and dosage changes	HbA1c, fasting capillary glycemia	0 and 12 mo	Relative to the control group, the intervention group exhibited greater glycosylated haemoglobin (HbA1) reduction [-2.2% (95%CI, -2.8%: -1.6%) *vs* -0.3 (95%CI, -0.8:0.2); P < 0.001] and greater fasting capillary glycaemia reduction [-20.1 mg/dL (95%CI, -31.9 mg/dL: -8.3 mg/dL) *vs* 4.3 mg/dL (95%CI, -13.4 mg/dL: 22.2 mg/dL); P = 0.022]

Brazil	Borges *et al*[51]	To evaluate effect of pharmaceutical care	Two group experimental	*n* = 71, 31 in control group and 40 in intervention group, > 18 yr old, T2DM	Individual visit with pharmacist monthly, patient education, dosage adjustment	Fasting glycemia, HbA1c	0 and 12 mo	A significant reduction in the levels of glycosylated haemoglobin was detected in patients in the pharmaceutical caregroup, and an average increase was observed in the control group
Bulgaria	Petkova *et al*[52]	To evaluate effectiveness of educational programme by pharmacists	Single group	*n* = 24, 31-75 yr, diagnosed T2DM	Educational Sessions with five teaching units over one month	Blood glucose levels, frequency of hypoglycemic Incidents	0, 1, 3 and 6 mo	Education of diabetic patients by pharmacists can decrease the economic cost of T2DM management and benefit patients. Blood glucose levels decreased from 8 to 7.2 mmol/L ($P < 0.05$)
Bulgaria	Tankova *et al*[26]	To evaluate effectives of a teaching program 1 to 2 yr after implementation	RCT	*n* = 560, 319 in experimental group, 241 in control group, Insulin treated T1 + 2DM	Geneva-Düsseldorf Education Session Model (consists of lessons on DM, practical training on self-control, injection techniques, preparing meals, construction of menu, physical exercise) education is conducted by team of doctors, nurses and rehab therapist using interactive approach	HbA1c, Well-being as measured by 22-item questionnaire	0, 12 and 24 mo	Structured teaching education program improves patient's well being. Improvement in glycemic control of educated patients as compared to control group ($P < 0.01$) and increase in overall wellbeing ($P < 0.001$)
Cameroon	Kengne *et al*[35]	To evaluate effectiveness of nurse-led care	Population based sample participants referred to either one of the 2 rural clinics or one of the 3 urban clinics	*n* = 225, 39 in rural clinic and 186 in urban, T2DM	Education, clinic visits, monitoring, follow-up	Mean fasting capillary glucose	0 and visit 6 (varied over 1110 patient-months)	Difference in mean levels of fasting glucose between baseline and final visit was 1.6 mmol/L ($P < 0.001$)
Cameroon	Labhardt *et al*[36]	To evaluate effectiveness of non-physician clinician facility care	Included all of the 75 clinics in central region of cameroon	*n* = 79, T2DM	Protocol-drive care by non-physician clinicians (nurses), diet and lifestyle education	Fasting Plasma glucose	0 and 2 yr	Fasting plasma glucose decreased -7.8 mmol/L ($P < 0.001$)
China	Liu *et al*[28]	To evaluate effectiveness of group visit and self management model	RCT	*n* = 176, 98 in intervention group and 78 in control group, T2DM, between 35-80 yr	12 1.5 h sessions on self management education, one-on-one visits with health care providers, including nurse, general practitioner and diabetes specialist	BMI, SBP, DBP	0 and 12 mo	No significant changes in BMI or DBP in either group, significant change in SBP in intervention group of 1.48 ($P = 0.04$). Larger studies need to be done to determined effects of group visits on blood glucose and other metabolic parameters
China	Chen *et al*[119]	To evaluate effectiveness of nurse diabetes intervention	Quasi-experiment, pre and post-test	*n* = 150, 75 in each control and case groups, > 65 yr, diagnosed T2DM, HbA1c > 8.5%	Self-management education with visits lasting 30 min each, telephone follow-up two weekly	BP, HbA1c, Weight	0 and 3 mo	Nurse-led education and consultation is effective in improving management in T2DM patients. HbA1c in case group changed -0.8% ($P < 0.001$) while the control group had no significant change

Iran	Sarrafzadegan *et al*[27]	To evaluate effect of comprehensive, community based healthy lifestyle program on cardiometabolic risk factors	Multi-stage cluster, 2 areas	*n* = 9032, 4179 in intervention area, 4853 in reference area, general population (htn, metabolic syndrome, diabetes, cardiac disease pts)	Public education through mass media, healthy nutrition, increased physical activity, tobacco control and coping with stress	Cholesterol, abdominal obesity, fasting blood glucose	0, 7 yr	Mean fasting blood glucose increased, but prevalence of abdominal obesity, htn, hypercholesterolemia and hypertriglyceridemia decreased significantly in intervention area ($P < 0.05$), no significant change in prevalence of diabetes
Iran	Farsaei *et al*[47]	To evaluate effectiveness of pharmacist-led education program	RCT	*n* = 172, diagnosed T2DM, HbA1c > 7%	Two educational sessions followed by weekly phone calls and appointments, medication consultation	FBS, HbA1c	0 and 3 mo	There is improvement in diabetes management by involvement of pharmacist in multidisciplinary health care team. HbA1c and FBS (-1.7% and -30.8 mg/dL) were decreased in intervention group ($P < 0.001$)
Jamaica	Less *et al*[53]	To evaluate effectiveness of involvement of LDFs	Two group experimental	*n* = 293, 158 in intervention group and 135 in control group, 25-75 yr, diagnosed T2DM	Educational Sessions during 3 monthly visits, self-monitoring forms	HbA1c, BMI	0 and 6 mo	Patient education by LDFs improved glycemic control of T2DM patients. HbA1c reduced from 0.6% in intervention group ($P < 0.001$) while comparison group had an increase of 0.6% ($P < 0.001$)
Jordan	Jarab *et al*[48]	To evaluate effectiveness of pharmacist-led pharmaceutical care intervention program	RCT	*n* = 171, 85 in intervention group and 86 in control group, > 18 yr, diagnosed T2DM for at least 1 yr, HbA1c > 7.1%	Medication consultation, lifestyle education, follow-up calls 8 weekly	FBG, HbA1c, BMI, Lipid Panel, BP	0 and 6 mo	Pharmacist-led pharmaceutical care led to an improvement in glycemic parameters. Intervention group had a mean reduction of 0.8% HbA1c verses a mean increase of 0.1% in the usual care group ($P = 0.019$). FBG in intervention group had a reduction of 2.3 mmol/L and the intervention group showed an increase of 0.9 mmol/L ($P = 0.014$)
Malaysia	Tan *et al*[33]	To evaluate effectiveness of structured diabetes education program	Single blind RCT	*n* = 164, 82 in control and intervention group, > 18 yr, diagnosed T1 + T2DM, HbA1c > 7%	Educational sessions once a month for 3 mo self-care practices, individual counseling with nurse and physician	HbA1c, SMBG frequency	0, 1, 2 and 3 mo	A self-management diabetes education program improves the well-being of diabetic patients. Intervention group had lower HbA1c than control group by the end of study (intervention group – $P < 0.001$, hbac decreased 8.75 ± 1.75; control group 9.67 ± 2.01)
Mexico	Gallegos *et al*[39]	To evaluate effectiveness of nurse-led education	Two group quasi-experiment	*n* = 45, 25 in experimental group and 20 in control group, diagnosed T2DM	6 Educational sessions lasting 90 min each, 20 individual counseling sessions lasting 30 to 90 min throughout 50 wk	HbA1c, psychological adaptation, diabetes care skills	0, 3, 6, 9 and 12 mo	Counseling and education model is an effective intervention to improve metabolic control in T2DM patients. HbA1c decreased from 10.36 at baseline to 8.04 ($P = 0.000$) while comparison group HbA1c levels changed from 9.44 to 9.77
Samoa	DePue *et al*[37]	To evaluate effectiveness of nurse-community health workers team intervention for diabetes management	Cluster rct	*n* = 243, 140 in usual care group, 104 in intervention group, > 18 yr, T2DM	Group visits and individual visits based on risk of patients	HbA1c	0 and 12 mo	Mean HbA1c was significantly lower among CHW participants, compared with usual care, after

South Africa	Price *et al*[40]	To determine long-term glycemic outcome of a structured nurse-led care	Single group, single center	*n* = 80, T2DM	Nurse led drug titration, structured empowerment based diabetes education	HbA1c, BMI	0, 6 mo, 18 mo, 2 yr, 4 yr	BMI at 6 and 18 mo was significantly higher than at baseline (both $P < 0.01$), but the 48 mo value was not significantly different from 0 mo. Compared with baseline, HbA1c falls were all significant ($P < 0.001$ for 6, 18 and 24 mo and $P = 0.015$ for 48 mo)
South Africa	Gill *et al*[41]	To determine effectiveness for a nurse-led intervention and education based program	Single group	*n* = 284, diagnosed T2DM	Self-management education, pictorial based education	HbA1c, BMI	0, 6 and 18 mo	Nurse-led protocol and education based intervention improve glycemic parameters in diabetic patients. HbA1c was 11.6% at baseline, but improved to 7.7% at 18 mo
Thailand	Wattana *et al*[42]	To evaluate effectiveness of self-diabetes management program	RCT	*n* = 147, 72 in control and 75 in experimental, > 35 yr, Diagnosed T2DM, FPG > 140 mg	120 min of small group diabetes education class, four 90 min group discussions and two individual home visit sessions by nurse educators	HbA1c, CHD risk, quality of life assessment	0 and 6 mo	A diabetes self-management program is effective in improving metabolic control for T2DM patients. HbA1c change was -0.68 in experimental group ($P = 0.029$) and 0.07 in control group
Thailand	Navicharern *et al*[43]	To evaluate effect of multifaceted nurse-coaching intervention	Quasi experiment, 2 group	*n* = 40, 20 in control and experimental group, T2DM	3 individualized sessions, 2 follow-up phone calls over 12 wk	HbA1c	0 and 3 mo	Mean average of HbA1c of the experimental group was significantly lower than that of the control group [x(exp) = 7.10, SD = 0.67 *vs* x(cont) = 7.72, SD = 0.97; $P \leqslant 0.5$]
Thailand	Suppapitiporn *et al*[45]	To evaluate effect of pharmacist led intervention	RCT	*n* = 360, 180 in control and experimental group each (divided into 4 groups), T2DM	Drug counseling, special medical containers, diabetes booklet (in experimental group, 1 group received only drug counseling, 2nd group received drug counseling + special medical containers, 3rd group received drug counseling + diabetes booklet, 4th group received all)	HbA1c, mean fasting glucose	0, 3, 6 mo	Most favorable glycemic outco me was the group that received all of the interventions; mean FPG was reduced from 147.46 ± 36.07 to 125.38 ± 31.12 mg% ($P < 0.000$) in 1st visit (3 mo later) and still reducing effect on the 2nd visit (6 mo later) mean FPG from 147.46 ± 36.07 to 130.21
Thailand	Oba *et al*[44]	To evaluate effectiveness of community participation prevention program in diabetes prevention	Single group, pre-post test	*n* = 160, > 35 yr, BMI > 23 kg/m^2, waist circumference > 80 cm (women) and > 90 cm (men), FBS 100-125 mg/dL, no baseline diabetes (but at risk patients)	Nutritional education provided by nurse practitioner, fitness schedule in daily exercise log	BMI, SBP, DBP	0, 1, 2, 3 mo	Average mean scores of the BMI ($P < 0.001$), SBP ($P < 0.01$) and waist circumference ($P < 0.01$) among persons who were at risk of DM after the intervention were lower than before intervention
Tunisia	Jenhani *et al*[32]	To evaluate effectiveness of education program on diabetes control	Pre/post-test experiment	*n* = 87, diagnosed T1 + T2DM, insulin usage	Six education sessions, interactive learning conducted by nurse and general practitioner	HbA1c, BMI, anxiety level	0 and 6 mo	Education program led to an improvement in diabetes control in patients. HbA1c decreased from 8.80% pre intervention to 7.62% ($P < 0.000001$)
Turkey	Mollaoğlu *et al*[25]	To evaluate effectiveness of nurse-led planned education	RCT	*n* = 50, 25 in experimental and control group, 18-65 yr, diagnosed T2DM	3 Educational Sessions 30-40 min each, home visit follow-ups	HbA1c, FBS, lipid panel	0, 1 and 2 mo	Regular, structured, repeated education improves glycemic parameters in T2DM patients, HbA1c and FBS levels changes were not statistically significant
Turkey	Turnacilar *et al*[46]	To evaluate effectiveness of pharmaceutical care program	Prospective longitudinal, cluster	*n* = 43, T2DM	6 pharmacy visits, drug counseling, weight control importance	Capillary whole blood glucose, BMI	0, 15, 30, 45, 60, 75, 90 d	Mean fasting blood glucose decreased from 167 to 128 mg/dL ($P < 0.001$)

Turkey	Kitiş *et al*[38]	To evaluate effect of home monitoring by public health nurse	Quasi experimental, single group, time series	n = 34, T2DM for at least 2 yr	Caloric calculation, exercise recommendations, medication compliance, monitoring blood glucose, education study group, booklets, 1st two months frequency of visits based on patients needs, with 2nd mo, visits every 2 mo	HbA1c, fasting blood glucose, postmeal blood glucose	0 and 6 mo	HbA1c decreased from 7.3% to 6.7% (P = 0.000), FBG decreased from 186 to 150 (P = 0.001), postmeal blood glucose decreased from 204 to 156 (P = 0.000)

T2DM: Type 2 diabetes mellitus; RCT: Randomized control trial; BMI: Body mass index; HbA1c: Hemoglobin A1c; LDFs: Lay diabetes facilitators.

Table 2 Diabetes management: Structured dietary change and exercise as main components (not lifestyle education)

Country	Ref.	Objective	Study design	Sample size/ characteristics	Components of intervention	Measurements	Outcome measures	Conclusion
Brazil	Rodrigues Silva *et al*[60]	To evaluate effect of rice bran fiber diet	Single group	n = 11, 45-60 yr old, controlled diabetes by diet or oral hypoglycemic agents, T1DM + T2DM	1 wk low fiber diet, 2nd week low fiber diet + rice bran, cross over	Mean fasting and post prandial glucose	Daily fasting and postprandial glucose	Mean fasting and postprandial serumglucose levels were reduced, but values of high fiber diet were significantly lower (P < 0.001) than that of the lower fiber diet
China	Sun *et al*[71]	To evaluate effectiveness of structured integrated intervention program	RCT	n = 150, Intervention group 100 and control group 50, 18-70 yr, BMI > 23 kg/m^2, T2DM	Nutritional counseling and meal replacement, physical activity instruction, education – monthly group lectures, sample meal plans with applications of meal exchanges and low glycemic index foods	FBG + insulin, HbA1c	0, 3 and 6 mo	An integrated intervention program can achieve improvements in glycemic control. Mean fasting blood glucose values at 24 wk were 7.4 ± 0.2 *vs* 8.9 ± 0.4 mmol/L (P < 0.001), intervention *vs* reference, respectively. No change in HbA1c in reference group, but a -0.8% change observed in intervention group (P < 0.001)
Costa Rica	Goldhaber-Fiebert *et al*[64]	To evaluate effectiveness of group-centered, community based public health intervention	RCT	n = 61, 33 in intervention group and 28 in control group, diagnosed T2DM	11 weekly nutrition classes 90 min each, triweekly walking physical activity sessions 60 min each	HbA1c, FBG	0 and 3 mo	Community-based, group-centered intervention including nutrition and exercise can improve glycemic control and is economically feasible. Change in FBG in intervention group change -19, control group 16 (P + 0.048). Change in HbA1c in intervention group -1.8, control group -0.4 (P = 0.028)
India	Pande *et al*[56]	To investigate effects of low/medium glycemic indexed Indian vegetarian snacks and meal plans on diabetics	Single group experimental	n = 15, 42-58 yr, diagnosed T2DM	Redesigned meal plan focusing on decreasing starches, lipids and increasing fiber	Blood glucose, HbA1c, lipid profile	0, 1, 2, 3 and 4 wk	Significant improvement in metabolic parameters was observed and can be improved if compliance to low/medium GI diet is continued. Blood glucose level of 173.6 mg% at baseline decreased to 137.8 mg% (P < 0.001), HbA1c of 8% at baseline decreased to 7.1% from baseline (P < 0.001)

India	Shenoy *et al*[62]	To evaluate effectiveness of aerobic walking program with pedometer and HRM	RCT	*n* = 40, 20 in control and 20 in intervention, 40-70 yr, diagnosed T2DM, Not enrolled in any other physical activity program	Timed walking schedule of target 150 min/wk to reach a 50%-70% maximum heart rate, pedometer, HRM	BMI, GWB	0 and 2 mo	Walking with a pedometer and HRM is more effective than walking alone and results in a better wellbeing for T2DM patients
India	Kosuri *et al*[70]	To evaluate effect of yoga on T2DM patients	Single group	*n* = 35, T2DM	40 d yoga camp with yoga exercises everyday	BMI, general well being	0 and 40 d	BMI decreased from 26.514 to 25.771 (P < 0.001) and there was also an improvement in total general well being
India	Agrawal *et al*[61]	To investigate effect of camel milk on glycemic control and insulin sensitivity	Two group experimental, crossover	*n* = 28, T2DM	Cow milk for non diabetic group, camel milk for diabetic group, followed by 3 mo washout period, with switch	FBS, HbA1c, HOMA-IR	0, 1 (run in period), 4 (camel milk period), 5 (washout period), 8 mo (cross over to cow milk)	HbAlc improved due to camel milk consumption (8.39 ± 0.64 to 7.27% ± 0.67%) whereas deteriorated in the case of cow milk (7.36 ± 0.66 to 8.26% ± 0.60%) in diabetic group
India	Misra *et al*[67]	To evaluate effectiveness of PRT	Single group	*n* = 30, diagnosed T2DM	Scheduled PRT training of six muscle groups (two sets, 10 repetitions each), 3 times/wk	HbA1c, blood glucose, lipid profile, BMI	0 and 3 mo	Moderate PRT is effective in improving metabolic parameters in T2DM patients and should be an integral part of their exercise regimen. HbA1c changed 0.54%, (P < 0.001), fasting blood glucose changed 2.7 mmol/L (P < 0.001)
India	Arora *et al*[68]	To evaluate effectiveness of PRT compared to aerobic exercise	RCT	*n* = 30, 10 in supervised PRT, 10 in control group and 10 in aerobic exercise group, 40-70 yr, diagnosed T2DM > 6 mo, inactive lifestyle	Scheduled PRT exercises of 3 sets of 10 repetitions for 2 times per week, aerobic exercise of walking 30 min/d three times a week	HbA1c, BP, BMI, lipid profile, GWB	0 and 2 mo	Metabolic parameters in T2DM patients improved more with PRT compared to aerobic exercise. HbA1c levels decreased (P < 0.05) both in the PRT group (7.57% to 6.23%) and in Aerobic Exercise group (8.11% to 6.66%)
Iran	Yazdanpanah *et al*[66]	To evaluate effectiveness of community based participatory diabetes care program	Single group, CBPR	*n* = 320, 30-65 yr, diagnosed T2DM, impaired fasting glucose	Nutrition classes 90 min each 2 d per week for 4 wk, structured physical activity 60 min sessions 3x a week for 13 wk	FBS, HbA1c, BP, lipid profile	0, 3 and 4.1 mo	Community-based participatory program is a feasible model for diabetes control. FBS decreased from 176 to 102 mg/dL (P < 0.01) and HbA1c decreased from 6.9 to 6.1 (P < 0.001)
Nigeria	Adeniyi *et al*[69]	To evaluate effect of 12 wk exercise program	Single group	*n* = 29, T2DM for min 6 mo, triglyceride levels > 1.7 mmol/L, waist circumference > 102 cm (men) or 88 cm (women) and BP > 130/85	Alternate day 45 min exercises (3 d in a week) for 12 wk, exercises included aerobic exercise, mobilization and resistance exercises	Fasting blood glucose, HbA1c	0, 2, 4, 6, 8, 12 wk	Improvement was observed in the fasting plasma glucose of both male (t = 8.059; P = 0.0001) and female groups (t = 13.007; P = 0.01)
Nigeria	Salau *et al*[57]	To evaluate effect of fruits and vegetables diet on selected hematological parameters	Single group	*n* = 30, T2DM	Two servings of diced fruit mix (100 g each) every day, 1 serving of edible green and leafy vegetables (100 g each) every day	ESR, hematocrit	0, 2, 4, 6, 8, 10 wk	ESR decreased from 49.40 to 32.8 (P < 0.05). Regular intake of fruits and vegetables can reduce cardiovascular risk factors in diabetic patients

Nigeria	Oli *et al*[55]	To evaluate effect of high carbohydrate diet	Single group	*n* = 160, weight not more than 10% above or below the mean weight for their age, sex and height, age at onset of diabetes > 30 yr, random blood glucose between 100 mL and 200 mg/100 mL, no ketonuria	250 g to 300 g of carbohydrate daily per patient depending on age and occupation	Mean fasting glucose	3 yr	Fifty-three patients (33.1%) achieved excellent control of their blood glucose (mean fasting blood glucose of 7.0 mmol/L or less); 38 patients (23.8%) achieved good control of their blood glucose (mean fasting blood glucose of 7.0-8.0 mmol/L); and 42 patients (26.3%) achieved fair control of their blood glucose (mean fasting blood, glucose of 8.0-9.0 mmol/L)
South Africa	van Rooijen *et al*[63]	To evaluate effectiveness of exercise intervention program *vs* a relaxation program	Single blind double intervention RCT	*n* = 149, 74 in relaxation group and 75 in exercise group, 40-65 yr, diagnosed T2DM for at least 1 yr	Home exercise program, fortnightly 45 min aerobics, 20 min tensing of muscles and relaxing for relaxation group, interactive group sessions, diet lectures	HbA1c, BMI, BP	0 and 3 mo	The exercise group did not impact the glycemic parameters greater than the relaxation group. HbA1c decreased -0.39 (P = 0.02) for exercise group
Thailand	Komindr *et al*[58]	To evaluate effect of long-term intake of Asian food with different glycemic indices	Single group cross over	*n* = 10, T2DM, b/w 32-60 yr	High glycemic diet or low glycemic diet was mainly glutinous rice or mungbean noodles, intermediate glycemic diet was solely white rice	HbA1c	2 mo	Ingestion of mungbean noodles (a low glycemic diet) without increasing fiber intake, can improve diabetic control and protein conservation in type 2 diabetes
Thailand	Chaiopanont[54]	To evaluate effect of a sitting and breathing exercise technique	Quasi-experiment, single group, pre and post-test	*n* = 50, 42-80 yr, diagnosed T2DM	Scheduled sitting and breathing techniques once a week for 30 min	Post Prandial glucose, FBS, BP	0, 1 and 2 wk	The somporn kantaradudsi-triamchaisri sitting and breathing techniques had a postprandial hypoglycemic effect in T2DM patients. Post prandial plasma glucose levels decreased from 19.26 mg/dL (P < 0.001) in the 2nd week to 17.64 mg/dL in the 3rd week (P < 0.001)
Turkey	Acik *et al*[65]	To evaluate effectiveness of education and lifestyle recommendations	Non-randomized cluster controlled trial	*n* = 80, 33 in standard diet, 28 in exercise + diet, 39 in control group, diagnosed T2DM	Nutritional counseling, structure physical activity schedule 3 times/wk	HbA1c, BMI, Blood Glucose	0, 1 and 2 mo	Diabetes education intervention program involving lifestyle modifications improves glycemic parameters. HbA1c in the diet + exercise group decreased from 9.9% to 7.9% (P = 0.001) and in the diet group, levels decreased from 7.8% to 7.5% (P = 0.001)
Mexico	Jimenez-Cruz *et al*[59]	To evaluate effectiveness of lower-higher-glycemic index mexican style diet	RCT crossover	*n* = 14, 35-75 yr, diagnosed T2DM	Pamphlets, detailed instructions on high-low GI foods, washout period of 6 wk with 6 wk periods of treatment alternating between low-GI period and high-GI period	FPG, HbA1c, BMI, lipid panel	0, 1.5 and 3 mo	A low-GI mexican style diet improves metabolic control in obese T2DM patients. HbA1c is lower in the low-GI period (8.1) than the high GI-period (8.6) P = 0.02

T2DM: Type 2 diabetes mellitus; RCT: Randomized control trial; BMI: Body mass index; GWB: General well being; PRT: Progressive resistance training; HbA1c: Hemoglobin A1c; GI: Gastrointestinal; PRT: Progressive resistance training.

found sustained glycemic control at 18 mo. Chen *et al*[75] evaluated the efficacy of a telehealth system with diabetes education and home blood glucose monitoring in China, and found significantly lower HbA1c in the experimental group at 1 year. One study evaluated nurse SMS and follow-up *via* telephone and found significant improvements in glycemic control at 3 mo[76]. One RCT assessed efficacy of delivering SMS messages as reminders to follow diet, physical activity and prescription adherence and found significantly lower mean fasting blood glucose and 2 h post-prandial glucose in experimental group at 12 mo[77]. An RCT in Iran found a significant improvement in glycemic control in the experimental group that received electronic education (chat rooms, personal feedback from physician online)[78]. Only 1 of the 9 studies integrating technology failed to find any significant improvement in glycemic control; it was conducted in South Africa and involved a phone buddy system[79]. This study evaluated the effectiveness of a peer support mobile-phone based self-management diabetes intervention in a scarce resource setting. Women were paired with a phone buddy for support and were questioned about health behaviors *via* SMS. Blood glucose increased by 3.3 points by the end of study, but women reported higher level of social coping and they continued to attend meetings even a year later[79].

Diabetes prevention

Ten studies were recognized as diabetes prevention studies. These studies varied vastly in terms of sample size, study design, measurement outcomes and results. Among the 10 studies classified as prevention studies, 7 were categorized under the DPP-like interventions, as shown in Table 4. Of all the prevention studies, 4 studies were RCTs[80-84], 3 were single group[85,86] and two group studies[87] and 1 was a non-randomized controlled trial[88]. Sample sizes ranged from a large size of n = 4747 in the Iran non-randomized cluster controlled trial by Harati *et al*[88] to a small size of n = 19 in the Thailand two group experimental study by Numbenjapon *et al*[87]. Follow-up period also varied vastly, from a minimum of 6 mo[82,86] to a maximum of 72 mo[83]. India contributed the largest number of studies with a total of 4; other study countries were China, Peru Brazil, Iran and Thailand. It is noteworthy that one of the Indian studies evaluated lifestyle education intervention in youth 15-17 years of age[82].

Among the 7 studies that reported on interventions that were most similar to the DPP integrating lifestyle education, all reported evidence of efficacy. There was a diverse range in personnel who delivered the lifestyle education from a mix of clinicians[87] to trained nutritionists[80-82] to community health workers[86]. All studies reported significant improvements in FBG[80,85,86], BMI[87], HOMA-BCF[82] or cumulative incidence[81,88]. Among the 3 interventions that integrated diet and exercise as main components, all reported clinically significant changes in outcomes, as shown in Table 5. Xu *et al*[84] had a sample size of 81 participants and examined the effectiveness of low-glycemic meal replacement and individualized eating instructions along with exercise recommendations during a span of 12 mo. Lindgärde *et al*[89] had a sample size of 59 participants and examined the effectiveness of structured supervised endurance training in a span of 6 mo. Both studies were RCTs and observed significant changes in fasting plasma glucose levels by the end of the study in the experimental groups[84,89]. Pan *et al*[83] was the most ambitious trial with a sample of 530, and follow-up period of 72 mo; they evaluated whether diet alone, exercise alone, and diet and exercise combined delayed development of diabetes; they found significant reduction in diabetes incidence in all three experimental groups, when compared to control.

DISCUSSION

There are many lessons that can be learned from this review. There is a wide range of diabetes prevention and management strategies in the developing world. We identified 66 studies in 20 different low and middle income countries; 56 out of the 66 studies reported on diabetes management, and the remainder reported on diabetes prevention trial. We aimed to (1) evaluate whether diabetes prevention and control interventions that are similar to DPP in low and middle-income country context are effective; (2) identify interventions that are substantively different from the DPP (with regard to intervention components); and (3) among this latter group, evaluate whether there is evidence of efficacy. With regard to diabetes management interventions that were similar to DPP there is overwhelming evidence to suggest that they are effective. Further, potentially lower-cost allied health professionals such as nurses and pharmacists can play central roles in delivering lifestyle and medication adherence education. Pharmacist led interventions in particular should be promoted in United States settings because of the strong evidence of efficacy and their impact on glycemic control documented in this review as well as a previous Canadian review[90]. Pharmacies are potentially more cost-effective and more accessible than other healthcare providers; they may also be able to deliver lifestyle education in addition to medication advice as seen is a Turkish and Jordan study reviewed here[46,91]. Indeed, United States insurers are recognizing the cost-savings of utilizing pharmacists for this role[92]. Further, the approach can be potentially translated to alternative ethnic-specific healthcare settings such as botanicas, for example, which are seen as an important healthcare options among United States ethic minority populations[93] who carry a disproportionate burden of diabetes[94-97].

Our review also highlighted the diverse approaches to structured dietary interventions in diabetes management with evidence of efficacy on improving outcomes such as HbA1c[59]. However, more research is needed in this

Table 3 Diabetes management: Technology assisted interventions

Country	Ref.	Objective	Study design	Sample size/ characteristics	Components of intervention	Measurements	Outcome measures	Conclusion
Bangladesh	Kibriya *et al*[72]	To evaluate effectiveness of HMBG	RCT	*n* = 64, 32 in each arm, T2DM requiring OHA/ insulin, 35-64 yr, completed secondary school education, high SES	Health Education Sessions, HMBG Practical Sessions for 2 d	FBG, HbA1c	0, 3, 6, 9, 12, 15 and 18 mo	HMBG + education is cost-effective in developing country. FBG decreased by 2.49 mmol (P = 0.007) and HbA1c decreased by 1.37% (P = 0.02) in experimental group. FBG decreased by 1.47 mmol (P = 0.051) and HbA1c lost significance after 18 mo of follow up in control group
Bulgaria	Kempf *et al*[73]	To evaluate effectiveness of SMBG on T2DM patients	RCT	*n* = 124, 63 in SMBG group, 61 in control group	Structured lifestyle guidance manual, 150 test strips with blood glucose meter	HbA1c	0, 12 wk, 18 mo	At 12 wk of intervention the SMBG group significantly improved glycated hemoglobin (HbA1c) levels [from 7.4 to 6.9 (P < 0.001)], whereas HbA1c reduction were not significant in the control group. At 1.5-yr follow-up, in the control group HbA1c increased again, reaching baseline values (7.5%). In the SMBG group HbA1c remained stable [6.9%(P = 0.0003 for trend)]
China	Chen *et al*[75]	To evaluate the functionality of telehealth system	Two group experimental	*n* = 64, 32 in experimental and 32 in control, T2DM	Telehealth device package with blood glucose meter for frequent monitoring according to recommendations, telehealth data analysis platform, telephone to contact health care professional, diabetes education	HbA1c	0 and 1 yr	HbA1c decreased from 9.5 to 8 in telehealth group (P < 0.001), while in the control group, there was no significant improvement in HbA1c
India	Shetty *et al*[77]	To investigate feasibility of SMS	RCT	*n* = 215, 110 in SMS group and 105 in control group, diagnosed T2DM > 5 yr, 10% < HbA1c > 7%	SMS once in 3 d as reminders to follow diet, physical activity and prescription adherence reminders	HbA1c, FBG, Lipid profile	0, 4, 8 and 12 mo	SMS communication is acceptable and it improved health outcomes for diabetic patients. Mean FPG (185 mg/dL to 166, P < 0.002) and 2h PG 263 mg/dL to 220, P < 0.002) levels decreased significantly in the SMS group. There was no significant difference in the mean HbA1c values in both groups
Iran	Zolfaghari *et al*[76]	To evaluate effect of nurse short SMS *vs* telephone follow-ups	RCT	*n* = 80, 39 in SMS group and 42 in telephone follow-up group, T2DM, used oral medications only	SMS group received 6 messages every week with info on exercise, medication compliance, diet adherence; Telephone group received at least 2x a week call for 1st month and then weekly for 2nd and 3rd month, each call lasting 20 min	HbA1c, BMI	0 and 3 mo	HbA1c decreased -0.93 (P < 0.001) for telephone group and -1.01 (P < 0.001) for SMS group. Both follow-up interventions can decrease HbA1c levels
Iran	Nesari *et al*[34]	To evaluate effect of nurse telephone follow-up	RCT	*n* = 60, 30 in each group, < 65 yr, HbA1c > 7%	3 d diabetes self care education group before intervention, then telephone follow-up 2x/week for first month and then weekly for 2nd and third months with 30 min duration	HbA1c	0 and 3 mo	The change in HbA1c level was significant for the experimental group after 12 wk but not for the control group (-1.87%, P < 0.001 for the experimental group *vs* -0.4%, P < 0.15 for the control group)

Iran	Moattari *et al*[78]	To evaluate effectiveness of electronic education	RCT	*n* = 48, 24 in experimental and 24 in control, diagnosed T2DM, insulin usage, ability to use website/ internet	Chat rooms, consultation service, educational films, personal file feedback from physician online	HbA1c, Lipid profile, FBG	0 and 3 mo	Electronic education program can be useful in improving metabolic parameters in T2DM patients sign differences. Change in HbA1c in experimental group was -2.03% ($P < 0.0001$) and -0.6 in control group. FBS change was -10.87 mg/dL ($P = 0.681$) in experimental group and -0.79 in control group
Malaysia	Ismail *et al*[74]	To evaluate effect of self-monitoring blood glucose	RCT	*n* = 105, 58 in intervention and 47 in control, T2DM, age 35-65 yr	Glucometer, health education, 2 d classes with demos of SMBG	HbA1c	0 and 6 mo	HbA1c level in the intervention group showed a statistically significant improvement of 1.3% ($P = 0.001$; 95%CI: 0.6-2.0), relative to the control group that underwent usual care
South Africa	Rotheram-Borus *et al*[79]	To evaluate feasibility of mobile phone-based peer support intervention	Single group	*n* = 22, diagnosed T2DM	Informational support meetings, weekly success sessions	BMI, blood glucose, Coping, Hours of sleep	0, 3 and 6 mo	Although the phone buddy system resulted in positive coping styles and better sleep, glucose levels increased in participants

HMBG: Home monitoring of blood glucose; RCT: Randomized control trial; T2DM: Type 2 diabetes mellitus; MS: Short message service; SMBG: Self-monitoring of blood glucose.

Table 4 Diabetes prevention: United States Diabetes Prevention Program like prevention interventions (allied health professionals and lay member facilitated)

Country	Ref.	Objective	Study design	Sample Size/ characteristics	Components of intervention	Measurements	Outcome measures	Conclusion
Brazil	Pimentel *et al*[80]	To evaluate effectiveness of NEP	RCT	*n* = 67, 24 in intervention group and 43 in control group, IGT + 1 other risk factor for T2DM	Individual sessions once per month and group counseling twice per month with nutritionist	HbA1c, fasting glycemia + insulin, postprandial glycemia + insulin	0 and 12 mo	Long-term NEP improves metabolic parameters for high-risk DM individuals. Intervention group had a decrease in fasting glycemia (-14.0%, $P = 0.03$), fasting insulin (-9.0%, $P = 0.05$), postprandial glycemia (-21%, $P = 0.02$), postprandial insulin (-71.0%, $P = 0.02$) and HbA1c (-24.0%, $P = 0.006$). No significant changes were observed in control group
India	Ramachandran *et al*[81]	To determine whether lifestyle modification could influence development of diabetes in IGT individuals	RCT	*n* = 531, 136 in control, 133 in lifestyle modification, 133 in metformin, 129 in lifestyle modification and metformin, 35-55 yr, IGT	Diet advice in reduction of calories, refined carbs and fats by dietician, exercise recommendations for at least 30 min of brisk walking each day for sedentary lifestyle, metformin initial dose 250 mg twice daily increased to 500 mg twice daily after 2 wk by physician	HbA1c, blood glucose	0, 6, 12, 18, 24, 30 and 36 mo	Lifestyle modification significantly reduced the incidence of diabetes in Asian Indians. Cumulative incidence of diabetes was 55% in 3 yr in control group, and it was significantly lower in all three intervention groups (LSM = 39.3%, MET = 40.5%, LSM + MET = 39.5%)
India	Balagopal *et al*[85]	To evaluate effectiveness of community-based lifestyle intervention on diabetes prevention	CBPR, single group	*n* = 850, 10-92 yr, village resident	Dietary advice from certified diabetes educator, stress relaxation techniques, physical activity promotion from physical education trainers, 10 one-on-one sessions with health messages	FBG, diabetes incidence, BMI, BP, nutrient composition of diet	0 and 7 mo	Educational intervention was successful in improving dietary patterns in individuals with pre-diabetes/diabetes. FBG levels decreased from 94.4 mg/dL to 91.2 mg/dL ($P = 0.045$)

India	Balagopal *et al*[86]	To evaluate effectiveness of community based diabetes prevention and management program	CBPR, single group	*n* = 1681, > 18 yr, village resident	Lifestyle modification, group and one-on-one counseling, 5 group sessions and 5 one-on-one encounters by community health workers	FBG, diabetes prevalence, BMI, BP, nutrient composition of diet	0 and 6 mo	Community-based participatory programs are a useful model for prevention and management of diabetes. FBG levels decreased from 96.26 mg/dL to 94.94 mg/dL (P < 0.001)
India	Singhal *et al*[82]	To evaluate effectiveness of repetitive nutrition education and lifestyle intervention on adolescents in North India	RCT	*n* = 106, Intervention had 56, control had 50, 15-17 yr	Individual counseling for parents on phone every month for 10 min each, lectures of 30 min each for 10 wk, individual counseling for student every week for 1 h on diet by trained nutritionist, lifestyle and physical activity for at least 30 min, trained student volunteers for dissemination of health messages	HOMA-IR, waist circumference, HOMA-BCF, DI	0 and 6 mo	The intervention model has a potential to prevent T2DM in Indian adolescents HOMA-BCF changed 56.7 in intervention group (P = 0.003) and 24.5 in control group (P = 0.002). Disposition index changed 30.3 (P = 0.003) in intervention group and 8.3 in control group (P = 0.01). No significant changes in fasting insulin and HOMA-IR were noted
Iran	Harati *et al*[88]	To evaluate effectiveness of lifestyle intervention in development of T2DM	Non-randomized cluster controlled trial	*n* = 4747, 2992 in control group, 1754 in lifestyle modification group, no baseline diabetes	Educational interviews and lectures, nutritional educational classes 4 d/wk, health volunteers distributed educational material	FBG, diabetes incidence, BMI, lipid profile	0 and 42 mo	Lifestyle interventions could decrease the risk of developing T2DM in the general population, not just high-risk patients. Incidence of diabetes in the control and intervention groups was 12.2 and 8.2 per 1000 person-years, respectively, with a relative risk reduction of 65% (P < 0.003). FPG change from baseline was -2.9 (P < 0.01)
Thailand	Numbenjapon *et al*[87]	To evaluate lifestyle modification vs combined treatment (lifestyle modification + metformin) to prevent diabetes	Two group experimental	*n* = 19, IGT, Fam Hx of T2DM	Monthly visit with nurse educator, nutritionist, physician and psychologist for 3 consecutive months, and then every 2 to 3 mo afterward	BMI, 2 h plasma glucose	1 yr	BMI and 2-h plasma level were significantly decreased after treatment in normal OGTT group (P < 0.05)

NEP: Nutrition Education Program; RCT: Randomized control trial; T2DM: Type 2 diabetes mellitus; BMI: Body mass index; BCF: Beta-cell function; DI: Disposition index.

area as all the studies had small sample sizes and only one study was an RCT[59] . More effort should be made to integrate structured dietary components into diabetes management programs such as in the promotion of low-glycemic diets, a recommendation consistent with a recent 2014 review on nutritional strategies to prevent and manage diabetes[98]. Also, taking into consideration the importance of intervention translation to low-resource settings and diverse populations, Oli *et al*[55] highlights the importance of evaluating the impact of diets that consist of readily available local foods and found excellent/good blood glucose control in the presence of high carbohydrate diets in their Nigerian sample. This finding is consistent with evidence to support that it is the quality of carbohydrates (*e.g.*, low *vs* high glycemic index), not quantity, which determines risk of diabetes[98,99].

The benefits of exercise on diabetes management is well-documented[100]. However, less in known about how the different forms of exercise compare with regard to efficacy in managing diabetes. The efficacy of alternative forms of physical activity such as PRT and yoga/relaxation, in comparison to aerobic exercise or no exercise should be further evaluated and studied in United States. In 2 RCTs reported in this review, one in

Table 5 Diabetes prevention: Structured dietary change and exercise as main components (not lifestyle education)

Country	Ref.	Objective	Study design	Sample size/ characteristics	Components of intervention	Measurements	Outcome measures	Conclusion
China	Pan *et al*[83]	To determine whether diet and exercise interventions will delay development of NIDDM in individuals with IGT	RCT	*n* = 530, control = 133, diet = 130, exercise = 141, diet + exercise = 126, > 25 yr, IGT	Diet plans, exercise recommendations with brochures on instructions on increasing leisure physical activities and counseling sessions on daily recommended food intake, weekly for one month, monthly for three months and once every three months by physicians and nurses	FBG, 2-h fasting glucose	0, 24, 48 and 72 mo	Diet and exercise led to a significant decrease in the incidence of diabetes in individuals with IGT. The diet, exercise, and diet-plus-exercise interventions were associated with 31% ($P < 0.03$), 46% ($P < 0.0005$), and 42% ($P < 0.005$) reductions in risk of developing diabetes, respectively
China	Xu *et al*[3]	Evaluate effectiveness of lifestyle intervention and meal replacement	RCT	*n* = 81, 41 in intervention, 40 in control, > 18 yr, IGR	Daily low-glycaemic meal replacement, individualized eating instructions, exercise recommendations, a dietician measured weekly intake and physician conducted medical evaluations	HbA1c, fasting plasma glucose, 1 hr plasma glucose	0 and 12 mo	HbA1c change was -0.12 ($P = 0.02$), 2 h plasma glucose change was -1.24 ($P = 0.02$), fasting plasma glucose change was -0.12 ($P = 0.001$) in intervention group, no significant changes were noted in control group
Peru	Lindgärde *et al*[89]	To evaluate feasibility of supervised endurance training	RCT	*n* = 59, 33 in control group and 26 in experimental, 25-64 yr, normal plasma fasting glucose	Structured training sessions, one per week in control group and three per week for experimental group for 60 min each approved by physiotherapist	BMI, FBG, $VO2_{max}$	0 and 6 mo	Supervised exercise training is a low cost safe therapy with favorable benefits. Plasma glucose levels decreased from 5.1 mmol/L to 4.1 mmol/L ($P < 0.001$) in experimental group

RCT: Randomized control trial; IGT: Impaired glucose tolerance.

India and the other in South Africa, significant decreases in HbA1c levels in PRT or relaxation groups were found and were comparable to the decreases found in HbA1c levels in the comparison aerobic exercise groups[63,68]. This finding is consistent with previous evidence[101,102].

Finally, the fields of public health and medicine have seen an explosion in mHealth both in the United States and abroad, particularly in low-resource settings[103-110]. mHealth broadly defined is "the use of mobile computing and communication technologies in health care and public health"[110]. This review identified several promising mHealth approaches with evidence of efficacy. Shetty *et al*[77] demonstrated efficacy of a SMS delivered reminder system to follow diet, physical activity and prescription adherence on mean fasting blood glucose in an RCT conducted in India. Similarly, in an RCT setting in Iran, Moattari *et al*[78] found significant improvement in glycemic control in the group the experimental group that received electronic education. This study created an electronic education system for patients with a personal online site with username and password where they could access their health care reports. Participants could also participate in a question/answer section where they received answers within 24 h. The health care team also sent recommendations at the end of every week to each participant *via* the online portal[78]. mHealth strategies promise greater cost-efficiency over face-to-face interventions because settings are participant's natural environment with reduced needs for space, staff, and training. According to one review, the biggest advantages of using mobile devices, and in particular mobile phones, for health are that these devices are personal, intelligent, connected, and always with people[111].

All diabetes prevention studies showed evidence of efficacy. It is notable that India led the world in the number the trials and further, is the only country that has tested trial in youth. Therefore, for future it is important to monitor progress in India and recognize their work as a resource for developing approaches in low and middle income countries as well a resource in developing cost-efficient approaches in more affluent countries. Among the DPP like interventions, as in diabetes management approaches, it is important to consider lower-cost allied health professionals as intervention agents delivering the lifestyle education as well as lay members of the community such as community health workers.

We should note limitations to our review. It is possible that the studies that we identified in this review do not comprise a representative sample of diabetes prevention and management efforts occurring in low and middle-income countries. Further, almost all studies selected reported favorable outcomes (63 of 66 studies) in the

management and prevention of diabetes. Therefore, there is a possibility that this review was subject to publication bias[112]. However, the objectives of our review were descriptive and qualitative in nature. We aimed to identify the range of intervention approaches to diabetes prevention and management and whether there was evidence of efficacy.

Diabetes is increasing throughout the world. There is an opportunity to test novel approaches to diabetes prevention and control using models developed in low-resource settings/countries. According to Narayan *et al*[14], we can apply lessons learned from the HIV/AIDS experience to the global epidemic of diabetes and non-communicable diseases in general: "Ironically, the lack of good health systems for noncommunicable diseases in many low- and middle-income countries may offer opportunities for testing innovative models in ways that cannot be done in high-income countries with mature systems".

Diabetes is increasing in the United States[113] and in countries that are the biggest contributors of immigrants to the United States such as Mexico, China, India and Philippines[114-116]. These immigrant populations often originate from countries where diabetes is also prevalent. There are 40 million immigrants in the United States, representing a twofold increase in just two decades (1990-2010), and a growth rate that is unparalleled in United States history[117]. Although Mexico has contributed the largest number of immigrants to the United States, recent data indicate that Asia has now replaced Latin America as the major region of origin for the foreign-born population in the United States. Among the newly arrived from Asia, Chinese-origin immigrants constitute the largest proportion[118]. Thus, lessons and approaches to diabetes prevention and management documented in this review are critically important to the development of approaches in the United States as well as other affluent countries where immigrants constitute a large proportion of the population.

COMMENTS

Background

Research on the efficacy of diabetes prevention and control efforts have been concentrated in the United States and Europe, but the burden of disease is felt around the globe. By limiting research to high-income countries the authors may neglect the potential for high- and low-income countries to learn from each other, and for leveraging global resources in the development of more cost-effective strategies. Building on the demonstrated efficacy of the United States Diabetes Prevention Program, this paper aimed to identify the newest approaches to type 2 diabetes prevention and control in the developing world context, to inform the design of approaches that can be translated to low-resource settings both in the United States and abroad.

Research frontiers

The review (1) evaluated whether interventions similar to the United States Diabetes Prevention Program (DPP) are effective; (2) identified interventions that are substantively different from the DPP (with regard to intervention components); and (3) among this latter group, evaluated whether there is evidence of efficacy. This methodologic approach allowed us to identify strategies that had evidence of efficacy in order to inform the design of future interventions and gaps in evidence that require further investigation.

Innovations and breakthroughs

A total of 66 studies from 20 developing countries were gathered with publication dates through September 2014. India contributed the largest number of trials (11/66). Of the total 66 studies reviewed, all but 3 studies reported evidence of favorable outcomes in the prevention and control of type 2 diabetes. The overwhelming majority of studies reported on diabetes management (56/66), and among these more than half were structured lifestyle education programs. The evidence suggests that lifestyle education led by allied health professionals (nurses, pharmacists) were as effective as those led by physicians or a team of clinicians. The remaining diabetes management interventions focused on diet or exercise, but the evidence to recommend one approach over another was weak.

Applications

While a wide range of approaches to diabetes exists, this review points to gaps in knowledge regarding efficacious approaches to diabetes prevention and management. It highlights the need for more large experimental studies of dietary and exercise interventions. Among these, more evidence is needed on exercise interventions comparing alternative exercise to aerobic, and on dietary interventions that compare quality of carbohydrates to quantity of carbohydrates. Also approaches using allied health professionals have promise and can potentially be more cost-effective. Finally, it is important to monitor diabetes prevention/control efforts in India as a considerable amount of research and approaches have been tested there.

Peer-review

This manuscript presents the newest approaches to diabetes prevention and control in the developing countries. It is a manuscript of potential interest.

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