Commentary

Impaired insulin exocytosis in chronic hepatitis C infection: contributory role of p38δ MAPK–protein kinase D–golgi complex axis

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Hepatitis C virus (HCV) infection and chronic hepatitis C (CHC) are associated with a measurable risk of insulin resistance (IR)/impaired glucose tolerance (IGT)/diabetes mellitus (DM). While loss of hepatic endocrine function contributes to liver cirrhosis in diabetic patients, onset and progression of IR/IGT to diabetes and exacerbation of incident hyperglycemia are ostensibly linked with chronic HCV infection. In this regard, the study by Chen J et al. appearing in Clinical Science (2020) (134(5) https://doi.org/10.1042/CS20190900) attempts to understand the mechanisms underlying the savaging effects of chronic HCV infection on insulin-producing pancreatic β-cells and hence diabetic onset. The study investigated the role of mitogen-activated protein kinase (MAPK) p38δ–protein kinase D (PKD)–golgi complex axis in impacting insulin exocytosis. It was inferred that an insulin secretory defect of pancreatic β-cells, owing to disrupted insulin exocytosis, to an extent explains β-cell dysfunction in HCV-infected or CHC milieu. HCV infection negatively regulates first-phase and second-phase insulin secretion by impinging on PKD-dependent insulin secretory granule fission at trans-golgi network and insulin secretory vesicle membrane fusion events. This commentary highlights the study in question, that deciphered the contribution of p38δ MAPK–PKD–golgi complex axis to β-cell dysfunction in CHC milieu. This pivotal axis offers a formidable therapeutic opportunity for alleviation of double burden of glucose abnormalities/DM and CHC.

Commentary

Chronic hepatitis C (CHC) virus infection is linked with an array of comorbidities, which is attributed to ectopic excursions of hepatitis C virus (HCV) [1,2]. Despite HCV being hepatotropic, its ability to assail extrahepatic tissues like pancreatic acinar cells and pancreatic duct epithelial cells underscores its extrahepatic tropism. Insulin resistance (IR) and diabetes mellitus (DM), inter alia, are regarded as extrahepatic manifestations of HCV infection to a certain extent. CHC is regarded as an independent risk factor for incident diabetes as it confers 2- to 3-fold increased odds of DM onset in general population [3–6]. This relates to HCV-associated induction or accentuation of IR that serves as a diabetogenic precursor and hence constitutes an elementary aspect of diabetes aetiology in CHC patients. Reciprocally, IR with a domineering presence in 30–70% of HCV patients and that of diabetes in 8–33%, act as independent predictors of liver-related mortality [7,8]. Hence, they are complicit in advancing HCV-related liver disease like hepatic fibrosis and inflammation to liver cirrhosis and hepatocellular carcinoma (HCC) as demonstrated in NHANES III study [9–12]. Although the cause–effect relationship between IR and HCV infection is as yet unclear, HCV eradication following standard therapy of pegylated interferon and ribavirin augurs well for IR amelioration in HCV-infected individuals [13,14]. IR attenuation is imperative as it affects the response to HCV therapy. This is evident from an
IR-associated increased odds of not achieving sustained virological response (SVR), a sentinel indicator of HCV eradication [13]. As regards type 2 DM (T2DM), a significant association between T2DM and CHC-linked HCC across all aetiologies of hepatic ailments has been reported [9–12]. In this connection, euglycemia with HbA1c level of <7.0 notably lowers the risk for HCC, keenly emphasizing the salutary effects of rigorous glucose control in HCV-affected individuals [14].

While the influence of HCV on IR (albeit not causal) is amply evident, its effect on insulin-producing pancreatic β-cells in CHC milieu has been less well explored. What predisposes β-cells to dysfunction in HCV infection or CHC milieu? Initial supposition of HCV triggering an autoimmune response to β-cells and its possible contribution to diabetes was refuted by a lack of significant difference in the frequency of glutamic acid decarboxylase (GAD) antibodies, antityrosine phosphatase autoantibody and islet cell antibodies (predominant of which is GAD with which HCV shares regional amino acid homology) among diabetic patients irrespective of HCV infection [15]. Mechanistic evidence suggests direct cytopathic effect on β-cells by HCV particles and imposition of morphological and functional defects [16]. Indeed, it is well maintained that insulin signaling pathway is quintessential for glucose sensing and islet β-cells are indispensable entities for glucose homeostasis as they abundantly express insulin receptors and insulin signaling proteins as compared with α cells. It is also firmly established that IR and insulin secretory defects prognosticate T2DM onset. Therein, it could be envisioned that HCV-induced impaired insulin secretory capacity primes β-cell dysfunction and eventuates in diabetes onset and progression into attendant complications in HCV patients [16]. Indeed, an interactive connection between HCV infection and diabetes appears at early stages of hepatic disease [15]. In this context, the study by Chen et al. (Clin. Sci. (Lond.) (2020) 134 (5): 529–542) assumes significance to diabetes was refuted by a lack of significant difference in the frequency of glutamic acid decarboxylase (GAD) antibodies, antityrosine phosphatase autoantibody and islet cell antibodies (predominant of which is GAD with which HCV shares regional amino acid homology) among diabetic patients irrespective of HCV infection [15]. Mechanistic evidence suggests direct cytopathic effect on β-cells by HCV particles and imposition of morphological and functional defects [16]. Indeed, it is well maintained that insulin signaling pathway is quintessential for glucose sensing and islet β-cells are indispensable entities for glucose homeostasis as they abundantly express insulin receptors and insulin secretory response ad-

It is well understood that an impaired glucose-stimulated insulin secretion (GSIS) is suggestive of an inadequate β-cell compensation to IR and prognosticates T2DM [18]. As a corollary, IR and insulin sensitivity (IS) constitute two faces of the same coin engaged in a reciprocal relationship. In normo-glucose tolerant (NGT) subjects, a quantitative relationship exists between IS and β-cell function [19,20]. IS follows a hyperbolic and reciprocal relationship with β-cell measures as fasting plasma insulin, first-phase insulin response, glucose potentiation slope and β-cell secretory response. Putative to this consideration, a modest change in IS causes a proportional and reciprocal change in insulin levels and response [19,20]. Therein, it would be more convincing to assess both homeostatic model assessment of insulin resistance (HOMA-IR), a surrogate measure of IR, and IS in the study models, so as to determine the effects of HCV infection on β-cell function. This would further consolidate the pervasive influence of HCV on IR, hyper-insulinemia, hyperglycemia and GSIS, all of which are pertinent to CHC-associated T2DM. Indeed, HOMA-IR, a predictor of non-response to antiviral treatment in HCV patients, has been shown to be associated with SVR in many studies [20]. Therein, in line with the study objectives, a combined assessment of IR and β-cell secretory response addresses the primary influence of HCV on β-cell function and survival. As regards IR status in the study population, the findings were in consonance with the previous studies, wherein HOMA-IR was elevated in CHC patients compared with controls [8,21]. It was also high in CHC individuals with DM and impaired fasting glucose (IFG) as compared with normal fasting glucose (NGF) subjects. Also, estimates of β-cell function, inclusive of fasting HOMA-β and oral glucose tolerance test (OGTT)-derived insulinogenic indices viz., IGI(1) and IGI(2) and that of composite measure viz., disposition index (DI) were lowered in CHC patients in IFG range as compared with normal fasting glucose (NGF) subjects. Employing OGTT-derived measures of insulin release like IGI(1) and IGI(2) that signify incremental insulin response to oral glucose outcompetes HOMA-β in assessment of β-cell function. This explains the absence of any discernible alteration in HOMA-β in the study subjects. Another caveat concerning the usage of HOMA-β index is that it is representative of steady state β-cell function and hence does not reflect dynamism of insulin synthesis and secretion [22,23]. Additional dynamic measures of insulin response including early insulin and C-peptide response to oral glucose viz., area under curve (AUC)(Insulin(0-30))/AUC(Glucose(0-30)), corrected insulin response (CIR), AUC(C-Peptide(0-30))/AUC(Glucose(0-30)), AUC(C-Peptide(0-120))/AUC(Glucose(0-120)) are superior to HOMA-β and could possibly serve as peremptory measures of insulin release and hence β-cell dysfunction in CHC patients [22,23]. In addition, DI, that quantitatively assesses β-cell secretory response to IR negatively correlates with metabolic syndrome that represents a deadly coalition of insulin resistance, hypertension, dyslipidemia and dysglycemia [24]. The usage of DI as a composite measure of IS and β-cell secretory response and as being reflective of β-cell compensatory response to IR in CHC-milieu in the current study is thereby vital. In the study in question, a
marked increase in IR and reciprocal decrease in IS in HCV-infected IFG subjects that progressively deteriorates in CHC patients with DM, is suggestive of hampered early-phase insulin secretion and loss of compensatory insulin activity. Perhaps, a thorou\[95\]h decline in GSIS accompanies IR that worsens with progression of impaired glucose tolerance (IGT) to overt T2DM.

The metabolic aberrations subsuming β-cell dysfunction correlated with histological alterations in pancreatic islets of CHC patients in the study, displaying large number of cavitites and disordered arrangement with affected acinar structures and fibrotic pancreas. This firmly contrasted the conserved histological features of normal islets in non-diabetic uninfected pancreatic head carcinoma controls. These observations were further recapitulated in C/O78 mice that were categorized into NGT, isolated IIFG (IIIFG), IGT+IIFG (prediabetic) and DM groups that in turn signifies β-cell dysfunction in CHC milieu. Assessment of time-course of HCV infection en route to diabetes onset revealed that early infection stage was itself conducive for a prediabetic state with coincident functional defects in islets and pancreas. The trajectory of chronic clinical manifestation involved progression of hepatic fibrosis and aggravation during 6–10 months post infection. This convincingly explains the morbid and concerted influence of hyperglycemia and CHC on an accelerated and inordinate progression of hepatic fibrosis to liver cirrhosis and HCC [10–12]. Nevertheless, prediabetic mice were preponderant in middle and later stages of infection than in early stage, furthering an idea of an association of chronicity of HCV infection with IFG state. These observations also concur with the proposition that HCV infection is an independent predictor of glucose abnormalities with chronic hepatitis [15]. This strengthens the proposition that β-cell dysfunction arguably determines the magnitude of T2DM pathology in CHC milieu. Taken together, disrupted β-cell dysfunction is seemingly customary to HCV infection, occurring even within an impaired range of FG and primarily hinders an early-phase insulin response.

To decipher the role of HCV in modulating insulin secretion in β-cells, hyperglycemic clamp studies to assess GSIS were performed in vivo in cohorts of HCV-infected and mock-infected C/O78 mice. GSIS is biphasic involving rapid and robust release of insulin in the first phase followed by a slow and sustained pulsatile release in second phase. In the study in question, in response to stimulatory concentrations of glucose, plasma insulin levels drastically reduced in acute phase of insulin secretion in HCV-infected C/O78 mice. Nevertheless, a notable recovery in insulin secretion was observed in NGT group of HCV-infected C/O78 mice, that ostensibly relies on compensatory response to IR by β-cells. In healthy individuals, it is of common occurrence that an augmented IR associates with a proportionally greater β-cell secretory response in a bid to maintain similar glycemia [25]. Also, pre-exposure of β-cells to insulin under isoglycemic conditions augments β-cell secretory response to glucose or GSIS by an order of 40%. Nevertheless, this response is affected under hyperglycemic or stimulated conditions [26]. The above observations were further recapitulated in in vitro in adult male C57BL/6 mice and human islets and MIN6 cells. This inhibitory response could however by rescued by telaprevir (VX950), a peptidomimetic inhibitor of the HCV NS3-4A protease. Consistent with this, perfusion assays in either isolated human and mouse islets or MIN6 cells also demonstrated diminished first and second-phase insulin release than in control islets and this effect could be corrected by VX950. The magnitude of reduction of insulin release could be evinced from diminished total insulin pools in HCV-infected MIN6 cells. Taken together, these results collectively indicate that HCV infection and CHC disrupt insulin secretion (both first and second-phase). This is evidenced from a linear decrease in insulin secretion with an increased HOMA-IR and stimulation with glucose, a trendline that deteriorates further with progression into diabetic range. An additional aspect that deserves investigation concerns the effects of obesity or varied body mass index values on GSIS, as visceral fat is diabetogenic and obese individuals are refractory to treatment [27]. Also, combined occurrence of obesity, diabetes and steatosis amplifies the risk of advanced fibrosis in HCV patients [28].

Does HCV directly inhibit insulin secretion in β-cells? In the capacity of a direct inducer of T2DM, HCV core protein has been shown to induce insulin receptor substrate (IRS)-1/2 degradation, suppressor of cytokine signaling 3 (SOCS3) up-regulation, c-jun N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) activation in hepatic tissues. It can also modulate the activity of transcription factors like PGC-1α, FOXO1 [29–31]. By down-regulating IRS-2, FOXO1 phosphorylation and nuclear exclusion, HCV-core protein precludes GLUT2-mediated hepatic glucose intake and insulin-driven shut down of gluconeogenesis [32]. As regards IR, HCV impinges on IRS-1–Akt–protein kinase B (PKB) signaling pathway, wherein it up-regulates serine312 phosphorylation of IRS-1 and inhibitory serine432 phosphorylation of PKB. An ensuing impairment in hepatic glucose uptake could only be reversed by inhibition of JNK signaling pathway [29]. Concerning pancreatic β-islets, the molecular mechanisms underlying HCV-induced reduction in GSIS and augmented IR have been less well known. In this context, the study in question conclusively demonstrated that the proposed insulin secretory defect, in part, hinges on reduced insulin exocytosis in HCV-infected β-cells. Substantiating this observation, insulin content or INS and Pdx1 mRNA levels remained virtually unaffected in HCV-infected MIN6 cells and islets. To decipher as to which step of HCV infection interfered with insulin secretory pathway in β-cells, secretagogues like α-ketoisocaproate, glibenclamide,
tolbutamide, carbachol and $K^+$ that act at different stages of stimulus-secretion coupling were used in static incubation assays with HCV-infected MIN6 cells. Insulin secretagogues induce depolarization of pancreatic $\beta$-cell membrane via outwardly directed $K^+$ channel activation resulting in opening of voltage-sensitive calcium channel that promotes $Ca^{2+}$ influx [33]. Following this, calcium sensor activation occurs by intracellular messenger viz., cyclic AMP elevation. Subsequently, insulin exocytosis eventsuate by protein phosphorylation and secretory granule fusion (SG) with the pancreatic acinar cell plasma membrane. The resultant observations of decreased insulin secretion following HCV infection in the study pointed towards defective insulin exocytosis.

In continuity, the impact of HCV infection on insulin exocytosis can be reliably assessed by membrane capacitance measurements of $\beta$-cells. This method harnesses the electrical excitability of $\beta$-cells that couples the fluctuations in blood glucose concentrations with inhibition or stimulation of insulin release through electrical signals. $\beta$-cell exocytosis is associated with an increased capacitance that is kinetically distinguishable by two component phases, that of early rapid and sustained slower phases [34]. In the study in question, insulin exocytosis was impeded as demonstrated by 2-fold reduction in membrane capacitance in HCV-infected single $\beta$-cells. A train of 10 depolarization steps from 70 to 0 mV evoked reduced responses in HCV-infected cells, demonstrating a 2-fold lower membrane capacitance relative to controls. This was restored by VX950, suggesting that HCV infection directly assails steps from 70 to 0 mV evoked reduced responses in HCV-infected cells, demonstrating a 2-fold lower membrane capacitance in HCV-infected single $\beta$-cells. Nevertheless, with respect to usage of dispersed cells in this study for capacitance measurements, there appears a caveat. This is predicated on (i) lower secretory capacity of isolated $\beta$-cells than in situ, (ii) counterintuitive increase in exocytosis rates (approximately four order of magnitude) compared to maximum rate of insulin secretion for limited periods that could possibly affect reporting of insulin secretion and (iii) the peremptory need for maintenance of spatial relationship between $Ca^{2+}$ and exocytotic machinery for stricter measurements of insulin release [34]. Therein, conducting measurements in situ in cells in intact tissue in a co-morbid milieu (as the current study) is warranted.

For further confirmation and consolidation of disrupted insulin exocytosis in HCV infection or CHC milieu, and its purported role in $\beta$-cell dysfunction, the mobility of insulin secretory granules (SGs) to the site of exocytosis in $\beta$-cell plasma membrane was explored by deploying total internal reflection microscopy (TIRF) imaging analysis using green-fluorescent protein-tagged insulin granules and TAT-conjugated Cy3-labeled syntaxin1 antibody. Vesicle exocytosis requires integration of plasma membrane-bound proteins with those of secretory vesicles. Insulin SGs customarily dock and fuse at numerous separate syntaxin-1 clusters in $\beta$-cell intact plasma membrane, colocalizing with synaptosomal-associated protein of 25 kDa (SNAP-25) clusters. The current study demonstrated that docked SGs were invariant between control and HCV-infected $\beta$ cells in basal unstimulated state as depicted by punctate fluorescence. Nevertheless, a situation inimical for insulin SG fusion at syntaxin-1 clusters in HCV-infected islets is presented by markedly reduced expression of SNARE proteins like syntaxin-1, SNAP-25, synaptophysin (Figure 1). Further, a parallel recording of cumulative fusion events indicated a thorough decline in spontaneous fusion events of pre-docked-SGs following a 3.3 mM glucose stimulation in HCV-infected $\beta$ cells as compared with controls. An ostensive inhibition of pre-docked and non-docked new-comer SGs from HCV-infected cells occurred following increased glucose stimulation with 16.7 mM in first phase GSIS. In second phase GSIS, a decrease in no-docked and short-docked newcomer SGs occurred. A direct effect on exocytotic reaction was observed owing to marked decrease in spontaneous fusion events in HCV-infected $\beta$ cells of pre-docked SGs. In general, initial phase insulin secretion requires docking and priming of SGs at the release site, accounting for the rate of exocytosis exceeding the docking rate thereby creating a partial deficit of docked SGs [35]. In second phase, a pulsatile release corresponds to the need for a balance between rate of exocytosis and docking of newcomer SGs. These considerations thereby indicate that HCV infection affects pre-docked and new-comer SGs (Figure 1). Notably, the fusion events underlying I and II phase GSIS in $\beta$ cells were consistent with hyperglycemic clamp. This could be necessarily linked to decreased membrane docking in T2DM, overriding the ability of glucose to accelerate granule docking in normal $\beta$ cells [35–37]. Also, acquisition of release competence by the new-comer SGs is slowed down. Membrane docking of SGs, which is imperative for GSIS is notably impaired in T2DM owing to downregulated expression of key docking-related proteins [35–37]. Abiding by the exocytosis dynamics, priming follows docking and limits insulin secretion [35]. Putative to priming events preceding insulin exocytosis, an interesting aspect that can be deliberated upon, as an extension to current study is transcellular protein interactions between $\beta$-cells [35]. In this regard, clustered neuroligin-2–expressing $\beta$-cells promote INS-1 $\beta$-cell proliferation and insulin content through prolonged transcellular protein interactions with subsequent enhancement of the submembrane exocytotic machinery [38]. As these interactions directly impact insulin secretion, it would be reasonable to elucidate the role of neuroligin-2 in $\beta$-cell dysfunction in HCV-associated diabetes.
Figure 1. Contributory role of p38δ MAPK–protein kinase D (PKD)–Golgi complex axis in inducing β-cell dysfunction in chronic hepatitis C virus (HCV) infection

Insulin-containing secretory granules (SG) arise from golgi complex (GC) by budding from trans-golgi network (TGN) in pancreatic β-cells. HCV-like particles associate with GC membranes and cause a general distortion of golgi compartment of β-cells. MAPK p38δ negatively regulates glucose-stimulated insulin secretion (GSIS) through inhibitory phosphorylation of protein kinase D (PKD) that hinders insulin secretion. Chronic hepatitis C is associated with an increased p38δ phosphorylation, with a consequent increase in PKD-inhibitory phosphorylation. The resultant decrease in PKD activity negatively affects insulin SG membrane fission at TGN due to lack of phosphorylation of key proteins (Arfaptin) of scission machinery involved in detachment of SG precursor from TGN by neck destabilization. Consequent to SG scission disruption, impairment of regulated insulin secretion occurs. In addition, insulin secretory vesicle exocytosis requires integration of plasma membrane-bound proteins (syntaxin-1, SNAP-25, synaptophysin) with those of secretory vesicles. Following glucose stimulation, pre-docked and non-docked new-comer SGs are inhibited resulting in reduced GSIS in HCV-infected β cells. Also, in HCV-infected islets, expression of syntaxin-1, SNAP-25, synaptophysin is markedly reduced thereby preventing insulin SG fusion. Pancreatic β-cell dysfunction ensues from disrupted insulin exocytosis and resultant impaired stimulated insulin secretion in HCV-infected β-cells.

As insulin is processed in golgi complex (GC) and packaged into transport vesicles, it is appropriate to consider the possible involvement of GC-related events in affecting insulin secretion in HCV-infected milieu. Insulin exocytosis requires fusion of insulin-containing secretory vesicles leaving from trans-golgi network (TGN) with β-cell membrane. The study in question averred that enhanced membrane fission at TGN in HCV-infected islet cells accounts for impaired exocytosis observed in capacitance measurements. Underlying this proposition, golgi markers giantin and GM130 displayed a characteristic crescent in HCV-infected β-cells, while they were diffusely distributed in mock cells. Also, immunofluorescence images with golgi tracker depicted tightened distribution in HCV-infected β-cells. These observations could concur with the ability of HCV to induce golgi fragmentation and morphological defects. This in turn is supported by the occurrence of virus-like particles close to membranes of GC [16,39] (Figure 1). Delving into the molecular antecedents of disrupted insulin exocytosis in CHC, MAPK p38δ-protein kinase D (PKD) emerged as a complicit axis. p38δ negatively regulates GSIS through PKD inhibition and exocytosis regulation. PKD acts as a pivotal regulator of stimulated insulin exocytosis, as p38δ-induced inhibitory phosphorylation of PKD attenuates stimulated insulin secretion. Therein, an improved glucose tolerance associates with p38δ deficiency owing to enhanced insulin secretion in β-cells [40]. The deleterious effects of high fat-feeding-induced
IR and oxidative stress-induced β-cell failure can also be averted by p38δ loss [40]. In CHC milieu, HCV infection upregulates p38δ expression as demonstrated in MIN6 cells. With an increased infection time course, an increased p38δ phosphorylation occurs, with a consequent increase in PKD-inhibitory phosphorylation and reduction in PKD-activating autophosphorylation (Figure 1). An obvious increase in insulin secretion ensues from p38δ knockdown under basal and glucose-stimulated conditions, both in mock and HCV-infected cells as compared with controls. p38δ thereby significantly contributes to HCV-associated β-cell dysfunction through inhibitory PKD phosphorylation. How does this molecular axis partake in impaired insulin exocytosis? A convincing link between HCV-induced MAPK p38δ-mediated attenuation of PKD activity and dwindling insulin secretory capacity is provided by altered golgi complex (GC) organization in HCV-infected β-cells [39]. A recent study outlined the key role of GC components in HCV maturation process during which PKD negatively regulates HCV secretion or release [41]. HCV infection perceptibly causes distortion and subsequent fragmentation of GC in β-cells. This, coupled with attenuation of PKD in HCV-infected cells disrupts insulin exocytosis and hence secretion (Figure 1). PKD is recruited to TGN to regulate the vesicular trafficking to plasma membrane by way of phosphorylating important mediators. PKD activity is essential for membrane fission at TGN as it phosphorylates Arfaptin-1 and dissociates it from ADP-ribosylation factor, a step crucial for neck destabilization and SG fission [42]. Disrupting this controlled mechanism of SG scission results in impairment of regulated insulin secretion with no effect on the release of other transport carriers [42] (Figure 1). A therapeutic application can thereby be envisaged in this direction by generating neutralizing antibodies for p38δ to aid in improved GSIS and hence amelioration of β-cell function in CHC milieu.

Thus, it can be comprehended from the current study that HCV-imposed β-cell dysfunction occurs not only in diabetes but also under IFG levels concomitant with decreased insulin secretory capacity. HCV infection negatively impinges on first and second-phase insulin secretion by direct disturbance of Ca2+-induced activation of insulin granule exocytosis. This correlates with increased p38δ MAPK expression and p38δ-mediated inhibitory phosphorylation of PKD. Based on these considerations, therapeutic opportunities presented by PKD–p38δ MAPK–GC axis could be explored for clinical management of those suffering from the double whammy of CHC and HCV-induced diabetes.

Competing Interests
The author declares that there are no competing interests associated with the manuscript.

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Abbreviations
CHC, chronic hepatitis C; DI, disposition index; GC, Golgi complex; GSIS, glucose-stimulated insulin secretion; HCV, Hepatitis C virus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; IS, insulin sensitivity; NFG, normal fasting glucose; NGT, normal glucose tolerance; PKD, Protein kinase D; SG, secretory granule; T2DM, Type 2 diabetes mellitus; TGN, trans-golgi network.

References

