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Provisional chapter

Introductory Chapter: Historical Perspective and Brief Overview of Insulin

Gaffar Sarwar Zaman

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1. Introduction

One of the oldest diseases of mankind is diabetes mellitus. It was only during the later part of the nineteenth and first half of the twentieth centuries that newer advances relating to the pathology, predisposing factors, management, course and complications of diabetes mellitus were discovered. Yet many more demanding solutions relating to the disease are still required. It has been seen that urbanisation and ageing of the population is definitely related to diabetes mellitus. But it is also true that diabetes mellitus affects all ages and all races. It has been estimated that around 400 million people will be affected by diabetes mellitus by 2030 AD. There are three principal forms of diabetes mellitus: type 1, type 2 and gestational diabetes mellitus (GDM). It has been seen that Finland has one of the highest incidence rates of type 1 diabetes mellitus. Type 1 diabetes is most likely a polygenic disease and has a number of potential risk factors. Type 2 diabetes is associated with the interaction of environmental factors and genetic factors. Impaired glucose tolerance (IGT), which has a great potential to be converted to diabetes mellitus, also carries cardiovascular and other risks. It has been seen that the important risk factors for the occurrence of diabetes are (i) changes in lifestyle due to urbanisation, (ii) hereditary, (iii) resistance to insulin, (iv) accumulation of fat around the waist rather than generalised obesity, (v) increasing age and (vi) ethnicity. It has been seen that long-standing diabetes mellitus is associated with an increased prevalence of macrovascular and microvascular diseases. Other chronic complications such as neuropathy and retinopathy are very common in diabetes mellitus.

2. Historical perspective of insulin

Although diabetes mellitus was always recognised as a distinct entity for more than 3000 years, its exact cause was not known until the twentieth century.

Till the early 1920s, many investigators were of the strong suspicion that diabetes was caused by a malfunction in the digestive system related to the pancreas gland. During that time the fatal disease was treated by a diet which was low in sugar and carbohydrates and high in protein and fat.

In those days, the patient usually died shortly after diagnosis, but the above diet allowed them to live for some years.

However, Best and Banting [1], **Figure 1**, two Canadians, provided a great relief to the world when they were able to isolate insulin from canines. They first produced diabetogenic symptoms in dogs and then with the help of insulin injections returned the dogs to normalcy. On the morning of November 14, 1921, they announced their discovery to the world. Then on January 23, 1922, they first injected Canadian 14-year-old Leonard Thompson with insulin and continued the treatment for diabetes mellitus.

Banting [2], **Figure 2**, by virtue of his tedious research, was able to create a pancreatic extract, which enabled him to gather thousands of islet cells. He then prepared extracts of insulin from these islets.

Initially, the insulin was tested on dogs, and it was able to regulate their blood glucose levels. Then in 1922 they tested it on Leonard Thompson, who became the first human being to be

Figure 1. Charles Herbert Best, CC, CH, CBE, FRS, FRSC, FRCP (February 27, 1899–March 31, 1978) and Sir Frederick Grant Banting, KBE, MC, FRS, FRSC, (November 14, 1891–February 21, 1941) (Source: [1]).

Figure 2. Sir Frederick Grant Banting, KBE, MC, FRS, FRSC (November 14, 1891–February 21, 1941) (Source: [2]).

given insulin. The first dose was a failure as it was not purified enough, but the second dose which was purified by James B. Collip proved to be successful.

Development of insulin was done further by Banting along with laboratory director John MacLeod, and both of them were awarded the Nobel Prize in Physiology of Medicine in 1923.

The first person who promoted the benefits of a low-carbohydrate diet was Banting [3], **Figure 3**, originally referred to as the 'Banting diet'. After almost a period of 150 years post his publication of the renowned booklet 'Letter on Corpulence', addressed to the public (in the year 1863), the Banting diet has been backed up by several clinical trials as being safe and effective for weight loss, and it is now finally being acknowledged as a beneficial diet for people with diabetes.

It should be noted that Banting was not a scientist, but a highly skilful carpenter. While he was young, Banting became overweight, and he was told by a doctor to exercise more. But it did not help him. He tried a variety of weight loss options but failed in almost all of them.

Then he met Harvey who told him to give up butter, bread, milk, beer, sugar and potatoes—i.e. foods which contained sugar and starch. After 5 months, Banting returned to normal weight and he was more agile.

Best [4], **Figure 4**, also helped Frederick Banting in discovering insulin in 1922 after he became Banting's assistant in the summer of 1921. After being awarded the Nobel Prize in 1923 with

Figure 3. William Banting (c. December 1796–March 16, 1878) (Source: [3]).

Figure 4. Charles Herbert Best, CC, CH, CBE, FRS, FRSC, FRCP (February 27, 1899–March 31, 1978) (Source: [4]).

J.J.R. MacLeod, Banting shared the prize money with Best and the rest of his team that were responsible for insulin being developed. Best was instrumental in doing the chemical tests to measure blood glucose levels while working with the team.

Thompson [5], **Figure 5**, was the first patient having diabetes to receive insulin injections on January 11, 1922. Almost facing death, Leonard survived for another 13 years. Leonard, who was diagnosed some years previously, was admitted in Toronto General Hospital.

He was severely diabetic and was coming in and out of a diabetic coma and was weighing only 65 pounds. It was Leonard's father who gave the consent that his son should be the first person to test insulin, which was never previously been tried on another human being.

Initially the impure form of insulin was unable to make any impact in Leonard's condition; however, a purer version of insulin made him survive and his parameters came back to normal.

One of the most unique approaches to diabetes treatment was provided by Proctor [6], **Figure 6**, in the early 1900s, as he concentrated on patients taking their own responsibility.

Joslin made his mother survive through diabetes for 10 years through a rigorous combination of exercise, meal planning and food management. He was the founder of Joslin Diabetes Center.

The 'starvation diet' was first proposed by Allen [7], **Figure 7**, who proposed it before the discovery of insulin to increase the life span of diabetes patients.

Figure 5. Leonard Thompson (Source: [5]).

Figure 6. Elliott Proctor Joslin, MD (June 6, 1869–January 28, 1962) (Source: [6]).

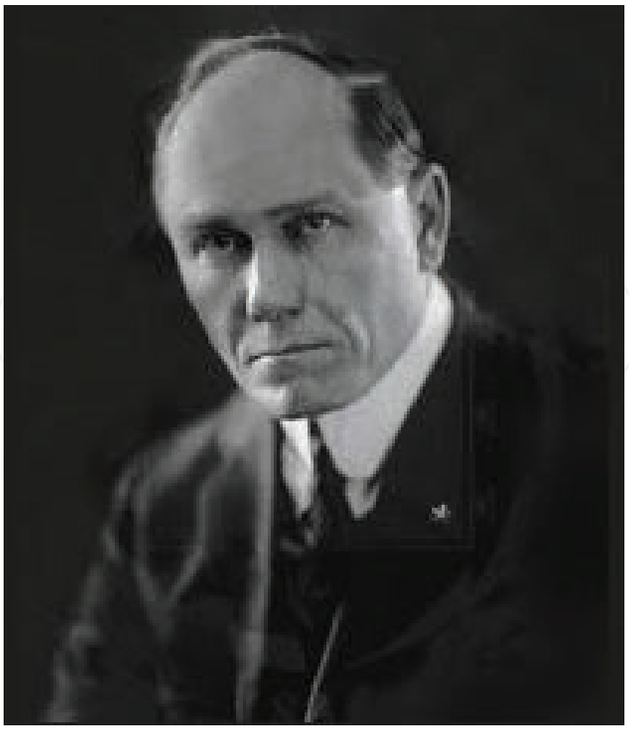

Figure 7. Frederick Madison Allen (1879–1964) (Source: [7]).

It was Allen, a physician, who first proposed that restriction in calorie intake and engaging oneself in regular exercise resulted in the prolongation of the life of insulin-producing beta cells.

3. Early research

Allen, who was born in Iowa, studied medicine at the University of California. He attended Harvard Medical School between 1909 and 1912, and thanks to his father's financing, he also published *Studies on Diabetes and Glycosuria* in 1913.

Insulin receptors were thoroughly studied mostly by Kahn [8], **Figure 8**. He spent most of his career investigating the role of insulin sensitivity in obesity and diabetes.

Kahn currently works as the Chief Academic Officer and Head of Joslin's Section on Integrative Physiology and Metabolism at the Joslin Diabetes Center.

He thoroughly investigated how cells are affected by insulin and the reason behind why only a particular group of cells develops insulin resistance, which is one of the main causes of type 2 diabetes.

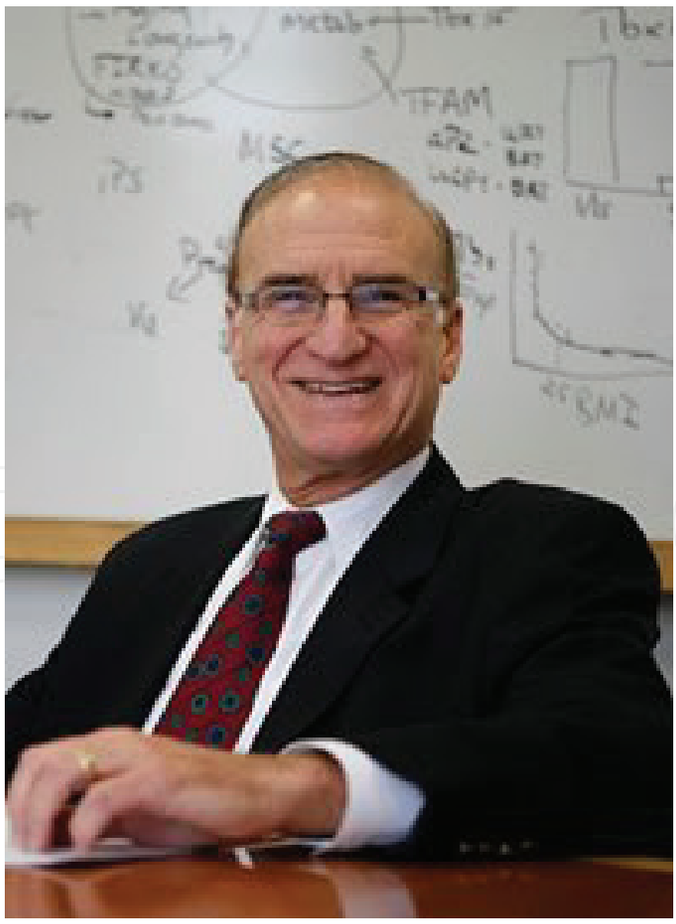

Figure 8. Carl Ronald Kahn (born January 14, 1944) (Source: [8]).

Kahn through his excellence in diabetes study became Research Director of Joslin and Associate Professor of Medicine at Harvard Medical School in 1981 and 1984. He was the first to discover the importance of the role of insulin actions in the brain and the causation of metabolic diseases by fat cells.

Bouchardat [9], **Figure 9**, is considered as the founder of diabetology, who helped in the treatment of diabetic patients before the creation of insulin in 1922. He was the first clinician who educated patients of diabetology to become aware of the disease. He also stressed the importance of exercise and urine glucose self-monitoring in the treatment of diabetes. He was the pioneer of advising against taking of sugars and starchy food to reduce glycosuria. He was also the first to hypothesise the location of diabetes in the pancreas.

Bouchardat wrote and published a number of books on diabetes, amongst them is his most well-known work 'De la Glycosurie ou diabète sucré, son traitement hygénigue'.

It was Collip [10], **Figure 10**, a biochemist, who played an important role in the production of the first insulin dose that was found to be appropriate for injection into humans.

The credit for the discovery of insulin goes to Banting and Best, but their extract was raw and failed to produce beneficial effects after being administered to Leonard Thompson, the first human to receive it.

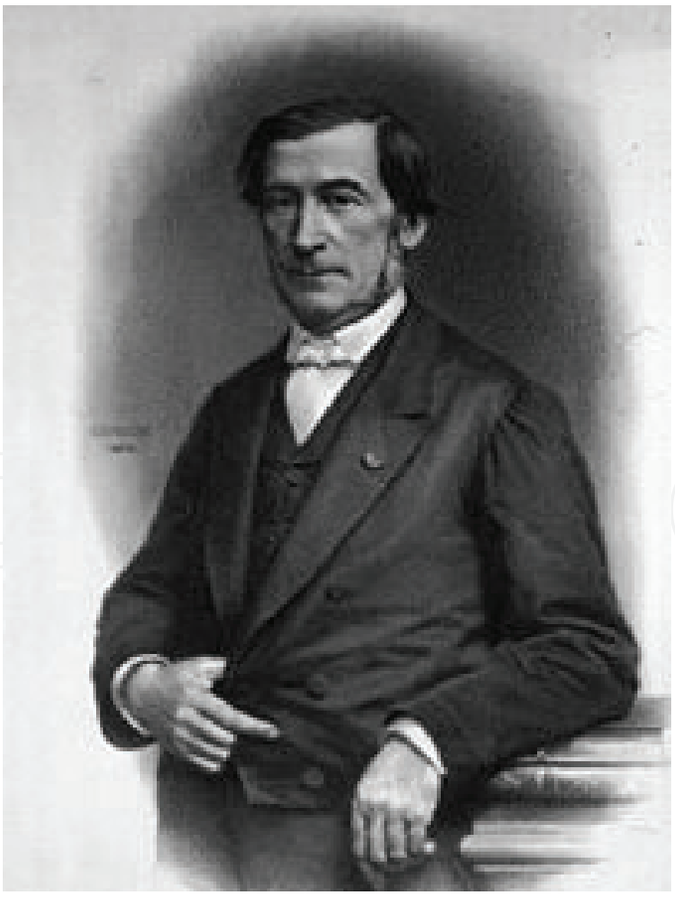

Figure 9. Apollinaire Bouchardat (July 23, 1809 – April 7, 1886), a French pharmacist and hygienist born in L'Isle-sur-Serein (Source: [9]).

Collip took up the job of purifying the extract within a period of 2 weeks, and it was again administered to Thompson. During the second time, the insulin extract stabilised Thompson's blood glucose levels, which saved his life.

Pancreatic diabetes was discovered by Minkowski [11], **Figure 11**. Minkowski studied at the University of Konigsberg before becoming a professor in Strasburg in 1888. Minkowski was a pioneer in the procedure of pancreatectomy in dogs.

White [12] was the pioneer of research into diabetic woman during pregnancy; it led to the White classification which is being used to assess diabetes during pregnancy (**Figure 12**).

This classification is still used today to differentiate between existing diabetes before pregnancy and gestational diabetes. The White classification established her in the diabetes history.

The secretion of insulin is an energy requiring process which involves the microtubule-microfilament system in beta cells of the islets of Langerhans. Varied numbers of mediators have been implicated in the release of insulin.

The level of glucose in the interstitial fluid regulates the activity of the beta cells. A sharp increase of 8–10 in the secretion of insulin usually occurs in response to an increase in plasma glucose from 70 to 150 mg/dl. During the same phase, a simultaneous decrease in the secretion of glucagon from A cell occurs. There is a greater B-cell response observed following oral as opposed to intravenous glucose administration. This is known as 'incretin' effect.

Of major importance, defects in the below-stated portions of the hormone's properties and journey in the body have been correlated and are most often related to hypertension, insulin resistance and type 2 diabetes [13–19].

Figure 10. James Bertram Collip, CBE, FRS, FRSC, FRCP, FRCPC (November 20, 1892–June 19, 1965) (Source: [10]).

Figure 11. Oskar Minkowski (January 13, 1858–July 18, 1931) (Source: [11]).

Figure 12. Priscilla White (March 17, 1900–December 16, 1989) (Source: [12]).

The journey of insulin can be divided into five stages, which can be related to insulin resistance and type 2 diabetes:

- Diabetic cell having defective insulin exocytosis [20–25].
- Defect in the vasoactive properties of insulin during insulin resistance, which includes capillary recruitment [22, 26–29].
- The GLUT4 translocation to the muscle membrane is diminished in humans [14, 22, 30–36].
- Decreased hepatic clearance of insulin [37] and CEACAM1 expression [38] in obesity.
- There is compromised glomerular function in obese people [22, 39–41].

Most of it is routed to the lysosome for degradation. But most of the degradation of the circulating hormone remaining after second pass through the liver continues in the kidney.

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References

[1] Best CH, Banting FG. https://southcoastherald.co.za/184174/canada-pioneers-diabetes-treatment/

[2] Banting FG. https://www.diabetes.co.uk/pioneers/frederick-banting.html

[3] Banting W. https://www.diabetes.co.uk/pioneers/william-banting.html

[4] Best CH. https://www.diabetes.co.uk/pioneers/charles-herbert-best.html

[5] Thompson L. https://www.diabetes.co.uk/pioneers/leonard-thompson.html

[6] Joslin EP. https://www.diabetes.co.uk/pioneers/dr-elliott-proctor-joslin.html

[7] Allen FM. https://www.diabetes.co.uk/pioneers/frederick-madison-allen.html

[8] Kahn CR. https://www.diabetes.co.uk/pioneers/ronald-kahn.html

[9] Bouchardat A. https://www.diabetes.co.uk/pioneers/apollinaire-bouchardat.html

[10] Collip JB. https://www.diabetes.co.uk/pioneers/james-collip.html

[11] Minkowski O. https://www.diabetes.co.uk/pioneers/oskar-minkowski.html

[12] White P. https://www.diabetes.co.uk/pioneers/priscilla-white.html

[13] Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: Insights into insulin action. Nature Reviews. Molecular Cell Biology. 2006;**7**:85-96. DOI: 10.1038/nrm1837

[14] Hoehn KL, Hohnen-Behrens C, Cederberg A, Wu LE, Turner N, Yuasa T, et al. IRS1-independent defects define major nodes of insulin resistance. Cell Metabolism. 2008; **7**:421-433. DOI: 10.1016/j.cmet.2008.04.005

[15] Odegaard JI, Chawla A. Pleiotropic actions of insulin resistance and inflammation in metabolic homeostasis. Science. 2013;**339**:172-177. DOI: 10.1126/science.1230721

[16] Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harbor Perspectives in Biology. 2014;**6**:a009191. DOI: 10.1101/cshperspect.a009191

[17] DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, et al. Type 2 diabetes mellitus. Nature Reviews Disease Primers. 2015;**1**:15019. DOI: 10.1038/nrdp.2015.19

[18] Samuel VT, Shulman GI. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. The Journal of Clinical Investigation. 2016;**126**:12-22. DOI: 10.1172/JCI77812

[19] Haeusler RA, McGraw TE, Accili D. Biochemical and cellular properties of insulin receptor signalling. Nature Reviews. Molecular Cell Biology. 2018;**19**:31-44. DOI: 10.1038/nrm.2017.89

[20] Ferdaoussi M, MacDonald PE. Toward connecting metabolism to the exocytotic site. Trends in Cell Biology. 2017;**27**:163-171. DOI: 10.1016/j.tcb.2016.10.003

[21] Gandasi NR, Yin P, Riz M, Chibalina MV, Cortese G, Lund P-E, et al. Ca^{2+} channel clustering with insulin-containing granules is disturbed in type 2 diabetes. The Journal of Clinical Investigation. 2017;**127**:2353-2364. DOI: 10.1172/JCI88491

[22] Tokarz VL, MacDonald PE, Klip A. The cell biology of systemic insulin function. The Journal of Cell Biology. 2018. DOI: 10.1083/jcb.201802095. http://jcb.rupress.org/content/early/2018/04/04/jcb.201802095/tab-article-info

[23] Lang DA, Matthews DR, Burnett M, Turner RC. Brief, irregular oscillations of basal plasma insulin and glucose concentrations in diabetic man. Diabetes. 1981;**30**:435-439. DOI: 10.2337/diab.30.5.435

[24] Hollingdal M, Juhl CB, Pincus SM, Sturis J, Veldhuis JD, Polonsky KS, et al. Failure of physiological plasma glucose excursions to entrain high-frequency pulsatile insulin secretion in type 2 diabetes. Diabetes. 2000;**49**:1334-1340. DOI: 10.2337/diabetes.49.8.1334

[25] Laedtke T, Kjems L, Pørksen N, Schmitz O, Veldhuis J, Kao PC, et al. Overnight inhibition of insulin secretion restores pulsatility and proinsulin/insulin ratio in type 2 diabetes.

American Journal of Physiology. Endocrinology and Metabolism. 2000;**279**:E520-E528. DOI: 10.1152/ajpendo.2000.279.3.E52e

[26] de Jongh RT, Serné EH, IJzerman RG, de Vries G, Stehouwer CDA. Impaired microvascular function in obesity: Implications for obesity-associated microangiopathy, hypertension, and insulin resistance. Circulation. 2004;**109**:2529-2535. DOI: 10.1161/01.CIR.0000129772.26647

[27] Clerk LH, Vincent MA, Jahn LA, Liu Z, Lindner JR, Barrett EJ. Obesity blunts insulin-mediated microvascular recruitment in human forearm muscle. Diabetes. 2006;**55**:1436-1442. DOI: 10.2337/db05-1373

[28] Keske MA, Clerk LH, Price WJ, Jahn LA, Barrett EJ. Obesity blunts microvascular recruitment in human forearm muscle after a mixed meal. Diabetes Care. 2009;**32**:1672-1677. DOI: 10.2337/dc09-0206

[29] Broussard JL, Castro AVB, Iyer M, Paszkiewicz RL, Bediako IA, Szczepaniak LS, et al. Insulin access to skeletal muscle is impaired during the early stages of diet-induced obesity. Obesity (Silver Spring). 2016;**24**:1922-1928. DOI: 10.1002/oby.21562

[30] Klip A, Ramlal T, Bilan PJ, Cartee GD, Gulve EA, Holloszy JO. Recruitment of GLUT-4 glucose transporters by insulin in diabetic rat skeletal muscle. Biochemical and Biophysical Research Communications. 1990;**172**:728-736. DOI: 10.1016/0006-291X(90)90735-6

[31] Zierath JR, He L, Gumà A, Odegoard Wahlström E, Klip A, Wallberg-Henriksson H. Insulin action on glucose transport and plasma membrane GLUT4 content in skeletal muscle from patients with NIDDM. Diabetologia. 1996;**39**:1180-1189. DOI: 10.1007/BF02658504

[32] Garvey WT, Maianu L, Zhu JH, Brechtel-Hook G, Wallace P, Baron AD. Evidence for defects in the trafficking and translocation of GLUT4 glucose transporters in skeletal muscle as a cause of human insulin resistance. The Journal of Clinical Investigation. 1998;**101**:2377-2386. DOI: 10.1172/JCI1557

[33] Sylow L, Jensen TE, Kleinert M, Højlund K, Kiens B, Wojtaszewski J, et al. Rac1 signaling is required for insulin-stimulated glucose uptake and is dysregulated in insulin-resistant murine and human skeletal muscle. Diabetes. 2013;**62**:1865-1875. DOI: 10.2337/db12-1148

[34] Aslamy A, Thurmond DC. Exocytosis proteins as novel targets for diabetes prevention and/or remediation? American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2017;**312**:R739-R752. DOI: 10.1152/ajpregu.00002.2017

[35] Foley K, Boguslavsky S, Klip A. Endocytosis, recycling, and regulated exocytosis of glucose transporter 4. Biochemistry. 2011;**50**:3048-3061. DOI: 10.1021/bi2000356

[36] Samuel VT, Shulman GI. Mechanisms for insulin resistance: Common threads and missing links. Cell. 2012;**148**:852-871. DOI: 10.1016/j.cell.2012.02.017

[37] Jung S-H, Jung C-H, Reaven GM, Kim SH. Adapting to insulin resistance in obesity: Role of insulin secretion and clearance. Diabetologia. 2018;**61**:681-687

[38] Lee W. The CEACAM1 expression is decreased in the liver of severely obese patients with or without diabetes. Diagnostic Pathology. 2011;**6**:40. DOI: 10.1186/1746-1596-6-40

[39] Kanasaki K, Kitada M, Kanasaki M, Koya D. The biological consequence of obesity on the kidney. Nephrology, Dialysis, Transplantation. 2013;**28**(Suppl. 4):iv1-iv7. DOI: 10.1093/ndt/gft098

[40] Spoto B, Pisano A, Zoccali C. Insulin resistance in chronic kidney disease: A systematic review. American Journal of Physiology. Renal Physiology. 2016;**311**:F1087-F1108. DOI: 10.1152/ajprenal.00340.2016

[41] Robbins DC, Shoelson SE, Tager HS, Mead PM, Gaynor DH. Products of therapeutic insulins in the blood of insulin-dependent (type I) diabetic patients. Diabetes. 1985;**34**:510-519. DOI: 10.2337/diab.34.5.510