Insulin is a Gift of Life for People With Diabetes

Anil K. Mandal¹,²,³*

¹Fulbright Scholar, Consultant in Nephrology, Putnam Community Medical Center, Palatka, FL, USA
²Courtesy Clinical Professor of Medicine, University of Florida at Gainesville, FL, USA
³Mandal Diabetes Research Foundation, 665 State Road 207, Suite 102, Saint Augustine, FL 32084, USA

ABSTRACT

Although Diabetes Mellitus (DM) or sugar diabetes was identified centuries ago, it was not known why this metabolic disorder develops until JR Macleod and Frederick Banting made the discovery. DM is due to deficiency of insulin produced by beta cells of the pancreas. Prior to this discovery and its application around 1921, many people with this disorder died from diabetic coma. Thus insulin made a milestone in the treatment of DM, in early part of the 20th century and it is the same today. However, commercialism prevails in the care of DM with too much twist in the therapy. It is now the norm to prescribe oral anti-diabetic agents in all adults with diabetes called Type 2 DM. Oral anti-diabetic drugs lower fasting blood glucose and HbA1c but not 2h postprandial blood glucose. The latter is related to diabetic complications. Thus, although patients are not dying from diabetic coma because of insulin but they are developing whole gamut of complications which have increased the morbidity and mortality in patients with DM. Thus the emphasis of this article is to resurgence the use of insulin as a gift of life for patients with DM and a therapy which permits a healthy and active life for them.

KEYWORDS: Diabetes; Diabetes Mellitus; Insulin; Pancreatic beta cells; Postprandial blood glucose; Fasting blood glucose; Glycosylated haemoglobin; Gift of life; Diabetic complications.

HISTORICAL PERSPECTIVE OF USE OF INSULIN

During May 1921, the Canadian researcher Frederick Banting under the supervision of John Macleod and helped by graduate student Charles Best attempted to extract the antidiabetic secretion from the pancreas of a dog. By 1922, the team was successful in obtaining a useful extract which they named insulin. They published their work in 1922 under the authorship of Banting and Best in which they reported on the successful use of a pancreatic extract for normalizing blood sugar levels in diabetic dogs. On January 11, 1922 they were presented with an opportunity to try pancreatic extract on a 14 year old boy named Leonard Thompson. This young Toronto resident had diabetes since 1919. He weighed 65 pounds and was about to sink into coma. He first received Banting’s and Best’s extract but he developed allergic reaction. Twelve days later, he received a second dose purified by James Collip. Thomson’s symptoms began to disappear; his blood sugar returned to normal and he was brighter and stronger. He lived for 13 additional years by taking insulin. He died at the age of 27 years due to diabetic complications.

One of the first people in Britain to benefit from the discovery of insulin was Sir Norman Purvis Walker, Treasurer of the Royal College of Physicians of Edinburgh. Walker was suffering from diabetes and by 1922 he was reduced to extreme emaciation and muscular weakness. When Walker received insulin, the effect was immediate.
Marie Krogh, wife of August Krogh, a noble laureate in physiology and medicine in 1921 was found to have maturity-onset diabetes. While in the USA in November 1922, together with the Danish physician H.C. Hagedorn, Krogh founded the Nordic Insulin Laboratory and Novo Nordisk Fund. Marie Krogh’s diabetes was successfully treated with insulin. In 1923, Eli Lilly & Co. in Indianapolis, Indiana started commercial production of insulin naming their product Isletin insulin.

In 1936, Zinc-protamine insulin was developed by the Canadians DA Scott and AM Fisher which presented a longer-acting insulin source. The Nordisk group in 1946 developed Neutral Protamine Hagedorn (NPH or Isophane insulin) which was neutral insulin with longer duration of action and which unlike the early protamine insulin, could be mixed with regular insulin. This was marketed in 1950. The same company researchers in 1953 developed the Lente insulins – Ultra lente, Lente and Semilente. In 1944, the standard insulin syringe was developed; helping to make diabetes management more uniform.

SMALL OR LARGE EXAMPLE OF THE BENEFIT OF THE USE OF INSULIN

The worst part of diabetes care is non-compliance in adhering to prescribed diet and insulin therapy. On the other hand, compliance of the patient and the support system in following prescribed diet and insulin therapy along with better understanding of the seriousness of diabetes complications without insulin treatment and taking full responsibility of the care along with the professionals will go long way in averting the complications of diabetes and staying healthy.

Here is an example of great compliance of the support system in rigidly following medical advice which has made it possible for healthy living of this 73 years old white male. He and his wife are residents of Montana, a northern state of the USA, lives in Florida during the winter months. He was first seen in March, 2014 by the author in consultation in a local hospital and thereafter followed regularly in one of author’s offices. In March 2014 he was found very lethargic and poorly conversing. He was noted to have uncontrolled diabetes and acute or chronic renal failure. He was treated with oral anti-diabetic agents consisting of glipizide and a DPP-4 inhibitor and angiotensin receptor blocker losartan. These therapies were discontinued and he was started on detemir insulin (Levemir®) 15 units after breakfast and dinner. Laboratory studies during hospital stay is shown in Table 1. After discharge he was seen in author’s office in April 2014. Medications consisted of detemir insulin 15 units after breakfast and dinner. Losartan 50 mg daily, paroxetine 20 mg daily, furo-rousulfate 300 mg PO TID, DPP4 inhibitor (onglyza®) 5 mg daily, glipizide 10 mg daily, furosemide 20 mg PO as required and spironolactone 25 mg PO as required.

Author’s action was to discontinue glipizide and DPP-4 inhibitor and Angiotensin Receptor Blocker (ARB) Losartan. Continue insulin detemir (Levemir®) 20 units after breakfast and dinner and hydralazine PO 25 mg BID was added. His next visit was in November 2014. Medications consisted of Novolin N 25 units morning and evening (could not afford Leveonm), calcitriol 0.25 mcg daily, ferrous sulfate as before, Vitamin C 500 mg daily, dipyridamide 75 mg 2 tablets morning and evening, hydralazine 25 mg PO BID. He did his laboratory. The results are shown in Table 2.

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>BUN (mg/dL)</th>
<th>Scr (mg/dL)</th>
<th>eGFR (ml/min)</th>
<th>Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Postprandial)</td>
<td>336</td>
<td>33</td>
<td>2.01</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 1: Shows serum glucose, renal function parameters, and hemoglobin levels.

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>BUN (mg/dL)</th>
<th>Scr (mg/dL)</th>
<th>eGFR (ml/min)</th>
<th>Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>99</td>
<td>22</td>
<td>1.35</td>
<td>52</td>
</tr>
<tr>
<td>2hPP</td>
<td>130</td>
<td>22</td>
<td>1.23</td>
<td>58</td>
</tr>
</tbody>
</table>

Table 2: Shows serum fasting and 2h post prandial (2hpp) glucose, renal function parameter, and hemoglobin (Hb) levels.

Glucose control has improved to normal levels with insulin. Renal function has improved to near normal levels, as well as haemoglobin levels. All these improvements are due to insulin therapy and exclusion of the use of ARB drugs, Losartan. Author’s action at this time was to discontinue dipyridamole as an additional cause of anaemia and double the dosage of iron. His next visit was in January 2015. He was very much conversing, feels happy as his wife. His medications were same as in the previous visit except dipyridamole. He did his laboratory. The results are shown in Table 3.

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>BUN (mg/dL)</th>
<th>Scr (mg/dL)</th>
<th>eGFR (ml/min)</th>
<th>Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td>97</td>
<td>20</td>
<td>1.40</td>
<td>53</td>
</tr>
<tr>
<td>2hPP</td>
<td>134</td>
<td>20</td>
<td>1.2</td>
<td>&gt;60</td>
</tr>
</tbody>
</table>

Table 3: Shows serum fasting and 2h post prandial (2hpp) glucose, renal function parameters, and hemoglobin levels.

Glucose control is normal with Novolin N 25 units twice daily. Blood pressure was 110/70 mmHg. Postprandial renal function is normal thus the goal is met. Haemoglobin is still low but increasing. However, iron reserve is normal and there was no evidence of occult gastrointestinal bleeding. Author’s action was to continue current therapy.

People with established diabetes whose blood glucose levels are higher than 200 mg/dL (>11.1 mmol/L) without treatment with insulin are at a high risk to develop complications acutely or in a protracted (chronic) fashion. It is important to remember that while acute complications reverse with intensive insulin therapy, chronic complications do not necessarily reverse even with intensive insulin therapy.
Thus the chronic complications of diabetes are reiterated here and how do these complications develop from pathological standpoint? The microvascular system is affected singularly and the vascular endothelial cells are the target organ for serious damage by high circulatory glucose milieu. These chronic complications are enumerated here but they are not in any particular order

• Retinopathy leading to impaired vision;
• Nephropathy leading to End Stage Renal Disease (ESRD) and dialysis;
• Unhealed foot ulcer or gangrene of toes or feet and amputation of a foot or a limb;
• Sexual dysfunction;
• Coronary heart disease leading to myocardial infarction and sudden death;
• Neurogenic bladder leading to urinary retention and recurrent urinary tract infection;
• Gastroparesis and paralytic ileus leading to recurrent vomiting, diarrhea, loss of nutrition and cachexia.

Thus, when patients present to a doctor’s office with one complication, careful examination may reveal additional complications. A variable degree of renal function impairment is a common accompaniment of many of the diabetic complications listed above. The renal failure most commonly defined by eGFR<60 ml/min is not necessarily and entirely due to uncontrolled diabetes but more often due to other concomitant therapy.

An important question is about the threshold of glucose level above which complications are likely to develop and below which complications are unlikely to develop. No definite answer is available to that effect. The reason is most outcome studies used glycosylated Haemoglobin (HbA1c) as the only glycemic parameter to validate the results. However, studies from Europe and other countries used 2h postprandial glucose above 200 mg/dL to determine cardiovascular morbidity and mortality. Here is a hypothetical question and fundamental laboratory research of author is presented later to clarify the hypothesis. Hypothesis is if glucose particles are injurious why doesn’t normal glucose level (70-99 mg/dL or 4.4-5.5 mmol/L) produce Endothelial cell (Ecs) damage but Ecs are damaged when they are treated with high glucose (above 200 mg/dL or 11.1 mmol/L). However, Ecs damage is largely mitigated when Ecs are treated with high glucose but insulin is added in the culture plate.7

Thus, this research finding of the author validates the clinical scenario that insulin treatment prevents renal failure and perhaps other diabetes complications. However, it should be stressed here that all author’s patients are treated with insulin and they all are living complication-free life.

The most important therapy for diabetes is obviously replacement therapy, which is insulin. Early insulin therapy with resultant satisfactory glucose control appears to spare or delay beta-cell damage and might even spare beta-cell function. Glucose control can be graded into three categories, according to this study.3

2-hour postprandial glucose levels can be easily obtained by ordering 2-hour postprandial Basic Metabolic Panel (BMP) after eating normal breakfast or lunch whichever is patient’s preferable meal.

• Satisfactory = <200 mg/dL (<11.1 mmol/L)
• Fair = 200-300 mg/dL (11.1-16.6 mmol/L)
• Poor = >300 mg/dL (>16.6 mmol/L)

Thus, satisfactory glucose control and frequent office visits to maintain the glucose control and adequate blood pressure and electrolyte and acid-base controls are prerequisites to prevention of complications strategy.4

Principle of Insulin Therapy

A variety of insulin preparations are available in the market. They are short (fast) acting, intermediate-acting and long acting insulin. It is important to understand that insulin therapy begins with long-acting insulin. There are two types of long-acting insulin available. They are Insulin Glargine (Lantus®) and Insulin Detemir (Levemir®). A recombinant DNA analog of human insulin, forms micro precipitates in subcutaneous tissue, delaying its absorption and prolonging its duration of action. Both have similar onset of action in about 4 hours and reach peak action in 8-9 hours. Effect decreases after 12 hours. There is no data to support or refute that either Lantus or Levemir will be effective for 24 hours in those with normal kidney function. Author prefers Lantus because he has more experience with that product. While Lantus or Levemir should be prescribed after breakfast and dinner (12 hours apart) in those with normal kidney function, once daily after breakfast is appropriate in those with reduced kidney function. Author typically prescribes 25 units after breakfast and dinner at the outset and increases dosage to achieve satisfactory glucose control. Although Lantus or Levemir alone can be used to achieve glycemic control and stabilize kidney function in some patients, other patients will need coverage of fast acting or regular insulin.

Fast-acting insulins

1) Insulin aspart (Novolog®)
2) Insulin Lispro (Humalog®)
3) Novolin®
4) Humulin®

While aspart or lisproinsulin are very rapid acting (action starts within 20 minutes), Humulin or Novolin R are fast and action starts within 30-40 minutes.
Intermediate-acting
1) NPH (Neutral Protamine Hagedorn)
2) Novolin N
3) 70/30 mixed insulin

NPH is uncommonly used in the USA, however, it may be prevalently used in other countries. A combination of Novolin R and Novolin N is effective in achieving glycemic control but the efficacy of mixed insulin is undocumented. The mixed insulin preparations are turbid which decreases efficacy, thus mixed insulin is not prescribed. It is important to know that insulin must be water color to be efficacious.

Satisfactory Glucose Control: Insulin Therapy

For patients with 2h postprandial or random glucose of less than 200 mg/dL author recommends a trial of diet control, avoid excesses (buffet lunch or dinner, parties) and regular exercise to reduce weight if overweight. Author does not recommend oral anti-diabetic agents as they reduce fasting blood glucose and elevate HbA1c but not 2h postprandial glucose which is critical in the development and progression of complications.5,6

Here is an isolated example of effect of insulin in lowering all the glycemic parameters: fasting glucose, 2h postprandial glucose and HbA1c. To that effect, metformin even in large doses is ineffective compared to insulin.

A 54 year old Cambodian female gave long history of diabetes and was treated with metformin 1000 mg twice daily. The results are shown in Table 4.

It should be noted that metformin didn’t affect HbA1c or 2h postprandial glucose. All glycemic parameters are high. Thus metformin was discontinued and she was started on Glargine insulin (Lantus) 25 units subcutaneously after breakfast and after dinner (12 hours apart). Her next office visit was in February 2011. The laboratory is shown in Table 5.

Lantus insulin effectively reduced fasting and 2hPP glucose levels, and HbA1c, and improved renal function.

Adversary to diabetes care is by not prescribing insulin to control hyperglycemia. Here is an outstanding example to that effect.

A 52 year African American male had his first office visit with the author in later part of December 2014. Prior to this office visit, he was admitted to a local hospital February, 2014; he was found to be diabetic and treated with regular insulin during hospital stay. Lisinopril was increased from 20 mg/day to 40 mg/day. Laboratory results upon admission and during hospital stay are shown in Table 6.

He was discharged from the hospital and followed by a primary care physician. He did not receive insulin after discharge from hospital until he reported to author’s office.

He gave history of uncontrolled diabetes which was first detected in year 2002. He was treated with metformin 1000 mg PO daily. He also gave history of hypertension. Medications at this visit included: hydralazine 25 mg x 3 TID, clonidine 0.1 mg x 2 TID, atenolol 50 mg daily, Lisinopril 40 mg daily, doxazosin 2 mg x 2 daily, calcitriol 0.25 mcg daily, amlodipine 10 mg daily, furosemide 40 mg daily, simvastatin 40 mg daily, Humulin N 10 units subcut at bedtime started. On examination he showed slight edema, blood pressure was 120/80 mmHg. A limited laboratory done in early December, 2014 showed random glucose of 421 mg/dL (23.3 mmol/L), serum creatinine of 3.14 mg/dL and eGFR of 25 ml/min. BUN was 53 mg/dL. Hemoglobin 9 g/dL.

Thus, he was found to have uncontrolled diabetes, Chronic Kidney Disease (CKD) stage 4, and anemia probably due to CKD and Lisinopril. Also he showed low vitamin D Level.

Therefore, actions included 1) Discontinue Lisinopril 2) reduce atenolol to 25 mg/ PO daily 3) start glargine insulin (Lantus) 25 units after breakfast and 25 units after dinner 4) increase Humulin N 10 units before each meal 5) order laboratory in one week. He returned to office in one week. He complained of erectile dysfunction but otherwise doing well. Laboratory is shown below (Table 7).
Glucose control improved, renal function remained low and anemia persisted. Authors action included 1) Increase Lantus insulin to 35 units after breakfast and 35 units after dinner and switch Humulin N to Humulin R 20 units before each meal and at bedtime. 2) Change furosemide to bumetanide 2 mg PO daily 3) Laboratory done on February 9, 2014 showed hemoglobin 9.3 g/dL. Glucose 258 mg/dL, serum creatinine 3.34 mg/dL with eGFR 23 ml/min. HbA1c 10.2% and uric acid 7.4 mg/dL. Thus his diabetes is still uncontrolled, renal function is low, CKD stage 4 with slight or no improvement. However, uric acid decreased to near normal level. Allopurinol is decreased to 150 mg PO daily and simvastatin is discontinued. Novolin R changed to aspart insulin 15 units before each meal and 10 units at bedtime. He will return to office, a laboratory will be done before office visit.

Glucose control is rapidly improving characterized by decrease in fasting and 2h postprandial glucose levels as well decrease in hemoglobin A1c. However he is markedly hyperuricemic and showing low CO2 level and high CPK suggesting rhabdomyolysis from use of simvastatin. He was admitted to a local hospital and treated with sodium bicarbonate infusion, demetir and aspart insulin for control of diabetes, chlorthalidone for control of hypertension and allopurinol for hyperuricemia. After 4 days of intensive therapy he felt happy and in parallel with significant improvement of laboratory findings. Findings are shown in Table 9.

His serum CO2 is 26 mmol/L, calcium is 9.3 mg/dL, phosphorus 4.2 mg/dL and uric acid decreased to 8.8 mg/dL. He was discharged from the hospital and followed in author’s office in 2 weeks.
trol. These are 1) finger stick practice using a glucometer and glucose strips 2) urine glucose testing. Although urine glucose testing is simple and cheap, but quantitative assay has not been developed to adjust insulin dosage based on urine glucose readings. On the other hand finger stick is painful and expensive, but it is prevalent methods of glucose monitoring at home to adjust insulin dosage. Most patients are educated to check sugar in the morning and night. These random levels may be important to determine glycemic level and adjust insulin dosage ups and downs according to their levels of glucose readings. Sugar testing is preferable 1-2 hours after a meal and at bedtime in order to adjust regular or fast acting insulin up or down. It is important to know that dosage of Lantus or detemir remains unchanged. If bed time glucose is high it will increase further through the night and will lead to nocturia and frequent wake up for bathroom visits, resulting in tiredness in the morning. This is a common feature in uncontrolled diabetes. Thus a bed time dose of regular insulin will minimize nocturia and ensure a restful night. Early morning glycemic surge giving rise to fasting hyperglycemia is not uncommon even in the most compliant patients. It is important to understand that this early morning hyperglycemic surge is conductive to good sleep; whereas an extra dose of insulin at bedtime may increase the risk of hypoglycemia, and waking up in early morning. However, nocturnal hypoglycemia may be minimized by eating a bed time snack consisting of a small sandwich and a glass of milk or juice.

PREVAILING COMMERCIALISM HINDERING TREATMENT OF DIABETES WITH INSULIN AND IS THE ROAD TO DIABETIC COMPLICATIONS

Given the discovery of insulin’s efficacy for treating diabetes, unfortunately therapy for diabetes has taken a different turn. This turn for the worse has been made possible by the influence of commercialism on our medical practices. Commercialism seems to prevail in “Diabetes care” more than any other illness and is orchestrated by drug companies in collaboration with professionals which sadly promotes profit over patients. Prevailing commercialism consist of promoting oral anti-diabetic drugs instead of insulin as a first line therapy for diabetes. This commercialism seems to be magnified by greedy industry and different medical societies.

In the current practice of diabetes, the most commonly drugs prescribed include metformin (antidiabetic agent) and Angiotensin Converting Enzymes Inhibitors (ACEI) or Angiotensin Receptor Blockers (ARB). Thus the worst commercialism is attributed to diagnosis of every adult with diabetes as Type 2 diabetes and automatic prescription of metformin and an ACEI lisinopril or an ARB drug losartan. Seldom does a provider discuss insulin treatment with the patient even though the glucose level may be 300 to 400 mg/dL (16.6 to 22.2 mmol/L). Lack of the knowledge of the professionals and overriding influence of the industry to prescribe metformin and state and federal regulations to prescribe ACEI/ARB drugs for renal protection in Type 2 diabetes continue to victimize the adult patients with diabetes.8 Regrettably, Los Angeles Times as of March 22, 2009 reported that over the last 15 years, the US rate of foot amputations from complications of diabetes has soared approaching 100,000 annually, according to studies and government statistics. To that effect, both parties are responsible. Professionals are not emphasizing adequate glucose control with insulin therapy. A recent report indicates that only 17% of diabetes patients take insulin; another 17% take a combination of insulin and oral agents; whereas 54% of diabetes patients are treated with oral agents.9

FUNDAMENTAL LABORATORY RESEARCH ATTEND TO BETTER UNDERSTANDING OF UTILITY OF INSULIN THERAPY IN DIABETES

In the laboratories of the author and colleagues, vascular endothelial cells were cultured for growth of the cells and then treated with normal concentration of glucose (90 mg/dL or 5 mmol/L) or high concentration of glucose (540 mg/dL or 30 mmol/L) for a period of 2 days, 6 days or 10 days. Additional cultured cells were treated with glucose of the same concentrations as above and insulin or with glucose, insulin and heparin.10 High glucose levels bathe all the cells in the body. But why does damage occur in some cell types? The answer is that most cells are able to reduce the transport of glucose inside the cells when they are exposed to high glucose levels, so that their internal glucose concentration remains constant. In diabetes, endothelial cells and mesangial cells cannot reduce transport of glucose inside the cells in state of high glucose levels in the blood. Therefore, complications that develop in diabetes must involve mechanisms of excessive amount of glucose inside the cells, rather than outside of the endothelial cells.11 We have shown that vascular endothelial cells are progressively damaged with increasing duration of exposure of the cells to high concentrations of the glucose but the damage is mostly mitigated with insulin treatment.10

CONCLUSIONS

1) Define diabetes or diabetes mellitus by obtaining fasting and 2h Postprandial (PP) metabolic panel. 2hPP glucose greater than 200 mg per dL establishes diabetes.
2) Insulin is the cornerstone of therapy in established diabetes. Insulin is a gift of life for diabetes, it prevents complications and allows subjects to live a healthy life except a few needle pricks a day
3) Blood pressure control is an integral part of diabetes therapy which reduces the risk of complications. Blood pressure control can be achieved with safe antihypertensive drugs
4) Use of ACEI/ARB drugs should be avoided. These drugs have no place in diabetes care.
5) Adequate glycemic control with insulin reduces proteinuria. Manipulation of proteinuria with ACEI/ARB invariably results in acute renal failure or chronic renal failure with progression to end stage renal disease.
REFERENCES


