Paradigm Academic Press
Journal of Innovations in Medical Research
ISSN 2788-7022
SEP. 2023 VOL.2, NO.9

Hypoglycaemia Among Diabetes Patients: A Preventive Approach

Devajit Mohajan[1] & Haradhan Kumar Mohajan[2]

[1] Department of Civil Engineering, Chittagong University of Engineering & Technology, Chittagong, Bangladesh

[2] Department of Mathematics, Premier University, Chittagong, Bangladesh

Correspondence: Haradhan Kumar Mohajan, Department of Mathematics, Premier University, Chittagong, Bangladesh.

doi:10.56397/JIMR/2023.09.05

Abstract

Hypoglycaemia is a low blood glucose concentration and an indicator of diabetes mellitus, and are associated with physical and psychological morbidity. It is a common, potentially avoidable consequence of diabetes treatment, and a major barrier to better metabolic control in diabetes. It is due to overtreatment of diabetes patients with insulin or sulfonylureas or glinides or also consumption of too little food or unplanned excessive exercise or physical activity. It is the acute complication of diabetes and is associated with considerable morbidity and mortality. It is important of the early recognition, treatment, and prevention of hypoglycaemia. Immediate treatment of severe hypoglycaemia is needed to avoid life threatening complications of the diabetic patients. In this study an attempt has been taken to discuss the aspects of hypoglycaemia of diabetes mellitus patients.

Keywords: Hypoglycaemia, blood glucose, diabetes, insulin

1. Introduction

If plasma blood glucose level is less than 4mmol/l irrespective of symptoms, usually the condition is called hypoglycaemia (hypos) (Boucai et al., 2011). Hypoglycaemia is considered as a decrease in blood glucose below the physiologic range. It is one of the most common problems related to diabetes (Briscoe & Davis, 2006). Except diabetes, it can occur as an epiphenomenon in many other serious diseases, and also due to irregular physical activities, such as starvation or after eating highly sugary meals and exercising. It is also seen in some medical conditions, such as insulinoma and renal disease (Gama, et al., 2003). Type 1 diabetes (T1D) that affects 5 to 15% of people with diabetes patients, are the most likely to have hypoglycaemia events, such as during treatment with insulin. Sometimes Type 2 diabetes (T2D) that affects 85 to 95% of people with diabetes patients, requires treatment with insulin, and occurs during severe hypoglycaemia (Donnelly et al., 2005). Hypoglycaemia diabetes patients, their families, and physicians all regularly share concerns about hypoglycaemia (IHSG, 2015). Hypoglycaemia may also occur in patients with non-insulin dependent diabetes patients. About 90% of all patients who receive insulin have experienced hypoglycaemic episodes. It is estimated that 2–4% of deaths occur in people with T1D due to hypoglycaemia (Laing et al., 1999).

The American Diabetes Association has defined hypoglycaemia in diabetes non-numerically as “all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm” (ADA, 2005). However, in severe hypoglycaemia blood glucose levels could be in 2.8 to 3.3mmol/l (Boucai et al., 2011; McCoy et al., 2012). If a glucose concentration levels are <3.0mmol/l (<54mg/dl) and <2.8mmol/l (<50 mg/dl), they are unequivocally hypoglycemic values, and cause defective glucose counter-regulation and impaired awareness of hypoglycaemia. The situation is considered to be clinically significant biochemical hypoglycaemia. It is the warning sign of falling blood glucose of a diabetes patient. It indicates that the patient is potentially in a

dangerous position. It is associated with mortality in patient due to cardiovascular risk (IHSG, 2017). More than 30% of patients with T1D and about 50% of T2D experience hypoglycemia, and among them 20% have episode of severe hypoglycemia. Of these, 22.3% were admitted to the hospital and about 0.1% of them had died (IHSG, 2015).

2. Literature Review

In any research, the literature review section is an introductory unit of research, where works of previous researchers are highlighted (Polit & Hungler, 2013). It provides an overview of existing knowledge, and allows a researcher to identify relevant theories, methods, and gaps in the existing research (Creswell, 2014). Jay H. Shubrook has realized that hypoglycaemia is a serious and common problem among diabetes patients who use insulin, yet the condition is often under-screened, unrecognized, and underreported. But most patients do not receive the regular ongoing screening, education, and training support to prevent and self-manage hypoglycaemia when it occurs (Shubrook, 2020). Thenmozhi Paluchamy has emphasized on causes and risk factors, recognition of symptoms, glucose regulatory and counter regulatory mechanism, management and prevention strategies of hypoglycaemia (Paluchamy, 2019).

Penny Tenzer-Iglesias and her coauthors have tried to improve diabetes mellitus related outcomes, including reducing the risk and consequences of hypoglycaemia, effective patient self-management. They have observed that physician-patient collaboration is vital to develop and modify a treatment plan acceptable to the patients (Tenzer-Iglesias et al., 2012). Afif Nakhleh and Naim Shehadeh have presented a comprehensive update on the treatment and prevention of hypoglycaemia in T1D and T2D patients. They have observed that to prevent hypoglycaemia, much effort must be invested in patient education regarding risk factors, warning signs, and treatment of hypoglycaemia at an early stage, together with setting personalized goals for glycemic control (Nakhleh & Shehadeh, 2021).

Markolf Hanefeld and his coauthors have studied on available mechanistic and clinical studies on the relationship between hypoglycaemia and cardiovascular risk. They have realized that there is an impact of hypoglycaemia on cardiovascular function and mechanistic link is multifactorial (Hanefeld et al., 2013). Monica Hermann and her coworkers have identified a lack of studies on prevention and management of hypoglycaemia in the older individuals' homes. They have aimed to treat and manage complex health conditions of hypoglycaemia in older individuals with diabetes (Hermann et al., 2021). Maja Baretić and Valeria Bralić Lang have shown that hypoglycaemia in T2D is still unsolved issue. They have wanted to investigate hypoglycaemia in T2D in participants treated with oral antihyperglycaemic agents using different glucose cut-off values and to explore influence of different therapies (Baretić & Lang, 2020).

Javier Morales and Doron Schneider have stated that hypoglycaemia is a common, potentially avoidable consequence of diabetes treatment and is a major barrier to initiate anti-hyperglycaemic therapy in efforts to achieve better glycemic control. They have seen that severe hypoglycaemia is associated with an increased risk of mortality, impairments in cognitive function, and adverse effects on patients' quality of life. Hypoglycemia burdens the healthcare system and adversely affects workplace productivity, particularly after a nocturnal event (Morales & Schneiderb, 2014).

3. Research Methodology of the Study

Research is a logical and systematic search for new useful information on a specific topic, which investigates to find solutions of scientific and social problems through systematic analysis (Rajasekar et. al., 2013). Methodology in any creative research is the organized and meaningful procedural works that follow scientific methods efficiently (Kothari, 2008). It provides the research design and analysis procedures to perform a good research (Hallberg, 2006). Research methodology is a strategy for planning, arranging, designing and conducting a fruitful research confidently (Legesse, 2014). It is the procedure to perform a research in a systematic and process oriented way that provides a guideline to the researchers to investigate a problem (Abbasi, 2015).

To prepare this paper, we have followed qualitative research approaches where we have tried our best to maintain the reliability and validity. The main body of the study is started through the discussion of categories and causes of hypoglycaemia. Then we have tried to analyze the symptoms and treatment of hypoglycaemia. In this paper, we have depended on the secondary data sources of optimization. The valuable materials for this study are included by the analysis of the published books of renowned authors. Additionally, we have studied the published papers of world famous printed journals and e-journals, handbooks, etc. to enrich this paper. We have searched internets and websites to collect valuable materials from Google scholars.

4. Objective of the Study

The crucial objective of this study is to discuss the hypoglycaemia of diabetes patients. Other non-crucial objectives of the study are as follows:

- to search the types of hypoglycaemia,
- to highlight on the causes and symptoms of hypoglycaemia, and
- to focus on the treatment of hypoglycaemia.

5. Categories of Hypoglycaemia

Hypoglycaemia was first discovered by Canadian biochemist James Bertram Collip (1892-1965) when he was working with Canadian medical scientist, physician, and painter Frederick Grant Banting (1891-1941) on purifying insulin in 1922. He observed that when he injected rabbits with a too large a dose of insulin, the rabbits began trembling, went into a coma, and then died (Collip, 1923). American Diabetes Association (ADA) workgroup on hypoglycaemia has introduced five categories of hypoglycaemia: i) severe hypoglycaemia, ii) documented symptomatic hypoglycaemia, iii) asymptomatic hypoglycaemia, iv) probable symptomatic hypoglycaemia, and v) relative hypoglycaemia (ADA, 2005). During severe hypoglycaemia the patient is quite unable to treatment himself/herself, and requires aid of another person to administer treatment. The situation is sufficient neuroglycopenia to induce seizure or coma (McCoy et al., 2012). Documented symptomatic hypoglycaemia bears common hypoglycaemic symptoms and measures plasma glucose of ≤70mg/dl (3.9mmol/l). Asymptomatic hypoglycaemia does not accompany by any typical symptoms of hypoglycemia but glucose measurement of ≤70mg/dl (3.9mmol/l). Probable symptomatic hypoglycaemia is self-reported symptomatic episode that is not verified by glucose determination. In this case symptoms of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration. Relative hypoglycaemia is symptoms associated with plasma glucose >70mg/dl (3.9mmol/l). Diabetes patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels 70mg/dl (3.9mmol/l) as plasma glucose concentrations decline toward that level (Hanefeld et al., 2013). Hypoglycaemia often occurs during sleep, which is called “nocturnal hypoglycaemia” and can range from asymptomatic to severe (McCoy et al., 2012; Bay et al., 2013).

According to the blood glucose level and manifestation of symptoms in response to low blood glucose level, hypoglycaemia can be categorized into Level I (mild), Level II (moderate), and Level III (severe). In Level I hypoglycaemia, the range of blood glucose level is 54–70mg/dl (3–3.9mmol/l). The symptoms at this level are tremor, palpitations, tachycardia, nervousness, sweating and hunger due to sympathetic nervous system is stimulation (Gehlaut & Shubrook, 2014; Paluchamy, 2019). In Level II hypoglycaemia, the range of blood glucose level is 40–54mg/dl (2.2–3mmol/l). The symptoms at this level are irritation, inability to concentrate, headache, lightheadedness, memory loss, confusion, numbness of the lips and tongue, slurred speech, lack of coordination, emotional changes, drowsiness, and double vision, or any combination of these symptoms due to impaired function of central nervous system (Paluchamy, 2019; ADA, 2020b). In Level III hypoglycaemia, the blood glucose level is less than 40mg/dl (2.2mmol/l) (Pettus et al., 2019). The symptoms at this level are disoriented behavior, seizures, stupor, or loss of consciousness. At this stage patients need help from another as they unable to function because of physical and mental changes (Paluchamy, 2019, ADA, 2020a).

Sometimes sudden and rapid falls of blood glucose from higher level to a lower but it is not too low to meet the hypoglycaemia level: ≤70mg/dl (3.9mmol/l). At this level brain started reacting to change and release of counter-regulatory hormones. This phenomenon is called “relative hypoglycaemia” and it is self-limiting. Brain will usually takes 2–4 weeks to readjust and to improve that relatively reduced circulating glucose levels, and within 2–4 weeks brain readjusts and improves the odd situation of glucose levels (Boyle et al., 1988).

6. Causes of Hypoglycaemia

When a diabetes patient takes too much medication, such as insulin or sulfonylureas or glinides tablets; also practices of low feeding, missed or late meal, enough low carbohydrate foods, and huge exercise; and during the adjustment of insulin dose, and hot weather may face low blood sugar (Cryer, 2008). Some illness, such as vomiting, diarrhoea, loss of appetite, consumption of excessive alcohol (alcohol inhibits glucose production), and fasting can cause hypoglycaemia (Clarke et al., 1991). Hypoglycaemia is the most common side effect of taking insulin. It is a widespread, erratic and possibly risky unexpected result of administer insulin for the T1D patients treatment. Even T2D patients face same condition when they have to treat with insulin (Cryer et al., 2009). Longer duration of diabetes, older age, history of recent severe hypoglycaemia, chronic kidney disease, and tight glycemic control are factors of an increased risk of hypoglycemia (Foster et al., 2018; ADA, 2020b).

Some additional causes of hypoglycaemia are excess alcohol consumption, obesity, elderly people, liver disorders, renal disease, adrenal insufficiency and pituitary insufficiency and leukemia. Another potential risk for hypoglycaemia is the use of β-blocker and ACE inhibitor medication in cardiac and hypertensive patients (Adler & Paauw, 2003).

In brief, hypoglycaemia typically happens when a person faces one or more of the unexpected situations, such as i) insulin doses are excessive, ill-timed or of the wrong type; ii) glucose utilization is increased during and

shortly after exercise without corresponding increase in food intake or decrease in insulin dose; iii) exogenous glucose delivery is decreased for missed meals or during the overnight fast, or as a result of gastroparesis or coeliac disease; iv) endogenous glucose production is decreased, for example, following alcohol ingestion; v) sensitivity to insulin is increased in the middle of the night or following weight loss, improved fitness or improved glycaemic control; and vi) insulin clearance is decreased as in renal failure (Moen et al., 2009).

Hypoglycaemia is a side effect of glucose lowering therapies, such as insulin, sulphonylureas, such as Gliclazide, Glipizide Glibenclamide, Glimepiride, Tolbutamide, and prandial glucose regulators (meglitinides), such as Nateglinide and Repaglinide. Metformin, Pioglitazone, Dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, sodium-glucose cotransporter-2 inhibitors, SGLT2 inhibitors and Glucagon-like peptide-1 (GLP-1) receptor agonists have a very low risk of causing hypoglycaemia. But when a patient uses a combination with the drugs mentioned above can cause severe hypoglycaemia (McCoy et al., 2012; van Dalem et al., 2016).

Physical activity and exercise are essentially beneficial, improve fitness and lower blood glucose levels. Hypoglycaemia can occur during, 1–2 hours after, or up to 17 hours after physical activity and exercise. But these can cause hypoglycaemia up to 24 hours afterward. Use of alcohol, particularly on an empty stomach, can cause hypoglycaemia, even a day or two later. Alcohol consumption increases the insulin secretion and makes the liver not to release the glucose effectively into the blood circulation. Hypoglycaemia also can occur when an individual asleep without meal for several hours (Lucidi et al., 2018).

7. Symptoms of Hypoglycaemia

Hypoglycaemia is an urgent complication of diabetes, and can happen suddenly. Symptoms of hypoglycaemia vary from person to person, and even vary for the same person under different circumstances. During hypoglycaemia the supply of glucose to the brain falls, and the brain cannot run its functions normally (Khunti et al., 2015). Usually two types of symptoms of hypoglycaemia are seen: adrenergic symptoms and neuroglycopenic symptoms. Adrenergic symptoms occur first as result of the effect of activation of the sympathetic nervous system, including the adrenal medulla. On the other hand, neuroglycopenic symptoms occur as a result of brain glucose deprivation (McAulay et al., 2001; Holt et al., 2017).

Some common symptoms of hypoglycaemia are unusual behaviors, hunger, fatigue, weakness, drowsiness, dizziness, headache, seizure, sweating, irritability, pale skin, anxiety, cravings for sweet foods, increase in appetite, increase in heartbeat, ataxia, nervousness, aggression, trembling, tachycardia, shakiness, lethargy, faintness, seizure, confusion, inability to concentrate, abnormalities, personality change, numbness of the lips and fingers, difficulty in speaking, slurred speech, blurry eyes with apparent vision or lack of coordination, double vision, loss of consciousness, inability to swallow, and coma. Some people are in hypoglycaemia, but face no symptoms (Morgan et al., 2018). When the patient is unconscious or unable to take oral glucose is considered as severe hypoglycaemia that can lead to seizures, coma, and even death (McCoy et al., 2012). Hypoglycaemia may happen during sleeping, and then the symptoms seems crying out or having nightmares; and feeling tired, irritable, confused after waking up (Hanefeld et al., 2013).

A patient's symptoms result from hypoglycaemia that may indicate insulinoma, can be identified by Whipple's triad (Whipple's criteria) that was first described by the American pancreatic surgeon Allen Oldfather Whipple (1881-1963). The essential conditions of Whipple's triad are (Whipple, 1938; Martens & Tits, 2014):

1) Symptoms known to be caused by hypoglycaemia, especially after fasting or intense exercise.
2) A low blood plasma glucose concentration measured at the time of the symptoms occurs.
3) Improvement of symptoms when the glucose is restored to normal.

8. Treatment of Hypoglycaemia

Hypoglycaemia is a potentially life threatening emergency that requires immediate and appropriate treatment. These symptoms can worsen if hypoglycaemia is not treated timely (Cowett & Loughead, 2002). When the symptoms of hypoglycaemia are seen in an individual, treatment must start through the history collection, physical examination, and the blood glucose checking and monitoring (Hicks et al., 2023). The hypoglycaemia patient should take 15-20g of a short-acting carbohydrate, which is the equivalent of one of the following: 5-7 glucose tablets or 120mls lucozade or 200ml pure smooth orange juice or 150ml coke or 20g glucose gel (Martyn-Nemeth et al., 2016). The patient then checks his/her blood glucose level after 10-15 minutes and takes more glucose until the blood glucose level is more than 4mmol/l or the symptoms have improved. At this situation the patient may take 15-20g of slower acting carbohydrates, such as a toast, one or two biscuits, a sandwich, a piece of fruit, a bowl of cereal, a glass of milk, etc. This will slowly release carbohydrate and maintain the blood sugar and the effects of the shorter acting carbohydrates will relief (Davidson, 1981; Kreider et al., 2017).

The American Diabetes Association (ADA) has provided the "15-15 Rule", which suggests consumption of 15 grams of a carbohydrate, followed by a 15-minute wait and re-measurement of blood glucose level to assess if blood glucose has returned to normal levels (ADA, 2005). Unconscious hypoglycaemia patients need assessment of Glasgow coma scale, monitoring of airway, breathing, and circulation, constant monitoring of blood glucose level. If a hypoglycaemia patient remains unconsciousness (hypoglycemic state) extends for more than five hours, it may cause permanent brain damage of the patient (Frier et al., 2014).

9. Conclusions

From this study we have observed that hypoglycaemia is one of the most feared complications of diabetes treatment, especially among insulin dependent diabetic patients. It is a common and possibly avoidable consequence of diabetes treatment. Medications, such as sulfonylurea, meglitinide, and basal insulin, particularly at doses >0.5units/kg per day, are common causes of hypoglycaemia. Moreover, drinking alcohol, and vigorous or unexpected exercise also increase the risk of hypoglycaemia. Sometimes it can cause hemiparesis, seizures, and coma due to severe hypoglycaemia, which is associated with increased mortality. It is wise and important to recognize and treat hypoglycaemia as early as possible to avoid the variety of consequences, and also can take appropriate action to prevent recurrence of hypoglycaemia. If a diabetes patient knows the risk factors, self-monitoring of blood glucose, selection of appropriate treatment regimens of hypoglycaemia, s/he can manage hypoglycaemia and can lead a healthy life. It is important and wise to avoid overtreatment, since this can only develop hyperglycaemia and its related complexities.

References

Abbasi, M. I., (2015). Marxist Feminism in Alice Walker's Novels: The Temple of My Familiar, Meridian and The Color Purple. PhD Thesis, National University of Modern Languages, Islamabad.

Adler, E., & Paauw, D., (2003). Medical Myths Involving Diabetes. *Primary Care, 30*(3), 607-618.

American Diabetes Association (ADA), (2005). Defining and Reporting Hypoglycemia in Diabetes: A Report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care, 28*, 1245-1249.

American Diabetes Association (ADA), (2020a). Comprehensive Medical Evaluation and Assessment of Comorbidities: Standards of Medical Care in Diabetes. *Diabetes Care, 43*(Suppl 1), S37-S47.

American Diabetes Association (ADA), (2020b). Glycemic Targets: Standards of Medical Care in Diabetes. *Diabetes Care, 43*(Suppl 1), S66-S76.

Baretić, M., & Lang, V. B., (2020). Hypoglycemia in Patients with Type 2 Diabetes Treated with Oral Antihyperglycemic Agents Detected by Continuous Glucose Monitoring: A Multi-Center Prospective Observational Study in Croatia. *BMC Endocrine Disorders, 20*, 35.

Bay, C., et al., (2013). Nocturnal Continuous Glucose Monitoring: Accuracy and Reliability of Hypoglycemia Detection in Patients with Type 1 Diabetes at High Risk of Severe Hypoglycemia. *Diabetes Technology & Therapeutics, 15*(5), 371-377.

Boucai, L., Southern, W. N., & Zonszein, J., (2011). Hypoglycemia-Associated Mortality is Not Drug-Associated but Linked to Comorbidities. *American Journal of Medicine, 124*(11), 1028-1035.

Boyle, P. J., et al., (1988). Plasma Glucose Concentrations at the Onset of Hypoglycemic Symptoms in Patients with Poorly Controlled Diabetes and in Non-Diabetics. *The New England Journal of Medicine, 318*(23), 1487-1492.

Briscoe, V. J., & Davis, S. N., (2006). Hypoglycemia in Type 1 and Type 2 Diabetes: Physiology, Pathophysiology and Management. *Clinical Diabetes, 24*(3), 115-121.

Clarke, W. L. et al., (1991). Multifactorial Origin of Hypoglycemic Symptom Unawareness in IDDM. Association with Defective Glucose Counterregulation and Better Glycemic Control. *Diabetes, 40*(6), 680-685.

Collip, J. B., (1923). History of the Discovery of Insulin. *Northwest Medicine, 22*, 267-273.

Cowett, R. M., & Loughead, J. L., (2002). Neonatal Glucose Metabolism: Differential Diagnoses, Evaluation, and Treatment of Hypoglycemia. *Neonatal Network, 21*(4), 9-19.

Creswell, J. W., (2014). *Educational Research: Planning, Conducting and Evaluating Quantitative and Qualitative Research* (5th Ed.). Sydney, Australia: Pearson.

Cryer, P. E., (2008). The Barrier of Hypoglycemia in Diabetes. *Diabetes, 57*(12), 3169-3176.

Cryer, P. E., et al. (2009). Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology & Metabolism, 94*(3), 709-728.

Davidson, M. B., (1981). *Diabetes Mellitus: Diagnosis and Treatment*. John Wiley and Sons, New York City.

Donnelly, L. A., et al., (2005). Frequency and Predictors of Hypoglycaemia in Type 1 and Insulin-Treated Type 2 Diabetes: A Population-Based Study. *Diabetic Medicine, 22*(6), 749-755.

Foster, E. D., et al., (2018). Clinical Islet Transplantation Consortium. Improved Health-Related Quality of Life in a Phase 3 Islet Transplantation Trial in Type 1 Diabetes Complicated by Severe Hypoglycemia. *Diabetes Care, 41*(5), 1001-1008.

Frier, B.M., Heller, S., & McCrimmon, R., (2014). *Hypoglycaemia in Clinical Diabetes* (3rd Ed.). John Wiley & Sons, Wiley Blackwell.

Gama, R., Teale, J. D., & Mark, V., (2003). Clinical and Laboratory Investigation of Adult Spontaneous Hypoglycaemia. *Journal of Clinical Pathology, 56*(9), 641-646.

Gehlaut, R. R., & Shubrook H. J., (2014). Revisiting Hypoglycemia in Diabetes. *Osteopathic Family Physician, 1*, 19-25.

Hallberg, L., (2006). The "Core-Category" of Grounded Theory: Making Constant Comparisons. *International Journal of Qualitative Studies on Health and Well-being, 1*(3), 141-148.

Hanefeld, M., Duetting, E., & Bramlage, P., (2013). Cardiac Implications of Hypoglycaemia in Patients with Diabetes: A Systematic Review. *Cardiovascular Diabetology, 12*, 135.

Hermann, M., et al., (2021). Hypoglycaemia in Older Home-Dwelling People with Diabetes: A Scoping Review. *BMC Geriatrics, 21*, 20.

Hicks, D., Hill, J., & James, J., (2023). *Hypoglycaemia in Adults in the Community: Recognition, Management and Prevention*. TREND-UK.

Holt, R. I. G., et al., (2017). *Textbook of Diabetes* (5th Ed.). John Wiley & Sons, Wiley-Blackwell.

International Hypoglycaemia Study Group (IHSG), (2015). Minimizing Hypoglycemia in Diabetes. *Diabetes Care, 38*(8), 1583-1591.

International Hypoglycaemia Study Group (IHSG), (2017). Glucose Concentrations of Less Than 3.0 mmol/l (54 mg/dl) Should be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care, 40*(1), 155-157.

Khunti, K., et al., (2015). Hypoglycemia and Risk of Cardiovascular Disease and All-Cause Mortality in Insulin-Treated People with Type 1 and Type 2 Diabetes: A Cohort Study. *Diabetes Care, 38*(2), 316-322.

Kothari, C. R., (2008). *Research Methodology: Methods and Techniques* (2nd Ed.). New Delhi: New Age International (P) Ltd.

Kreider, E. K., Pereira, K, Padilla, B. I., (2017). Practical Approaches to Diagnosing, Treating and Preventing Hypoglycemia in Diabetes. *Diabetes Therapy, 8*(6), 1427-1435.

Laing, S. P., et al., (1999). The British Diabetic Association Cohort Study, II. Cause-specific Mortality in Patients with Insulin-Treated Diabetes Mellitus. *Diabetic Medicine, 16*(6), 466-471.

Legesse, B., (2014). *Research Methods in Agribusiness and Value Chains*. School of Agricultural Economics and Agribusiness, Haramaya University.

Lucidi, P., et al., (2018). Prevention and Management of Severe Hypoglycemia and Hypoglycemia Unawareness: Incorporating Sensor Technology. *Current Diabetes Reports, 18*(10), 83.

Martens, P., & Tits, J., (2014). Approach to the Patient with Spontaneous Hypoglycemia. *European Journal of Internal Medicine, 25*(5), 415-421.

Martyn-Nemeth, P., et al., (2016). Fear of Hypoglycemia in Adults with Type 1 Diabetes: Impact of Therapeutic Advances and Strategies for Prevention: A Review. *Journal* of *Diabetic Complications, 30*(1), 167-177.

McAulay, V., Deary, I. J., & Frier, B. M., (2001). Symptoms of Hypoglycaemia in People with Diabetes. *Diabetic Medicine, 18*(9), 690-705.

McCoy, R. G., et al., (2012). Increased Mortality of Patients with Diabetes Reporting Severe Hypoglycemia. *Diabetes Care, 35*, 1897-1900.

Moen, M. F., et al., (2009). Frequency of Hypoglycaemia and Its Significance in Chrinoc Kidney Disease. *Clinical Journal of the American Society of Nephrology, 4*(6), 1121-1127.

Morales, J., & Schneider, D., (2014). Hypoglycemia. *The American Journal of Medicine, 127*(10A), S17-S24.

Morgan, R. K., Cortes, Y., & Murphy, L., (2018). Pathophysiology and Aetiology of Hypoglycaemic Crises. *Journal of Small Animal Practice, 59*(11), 659-669.

Nakhleh, A., & Shehadeh, N., (2021). Hypoglycemia in Diabetes: An Update on Pathophysiology, Treatment, and Prevention. *World Journal of Diabetes*, *12*(12), 2036-2049.

Paluchamy, T., (2019). Hypoglycemia: Essential Clinical Guidelines. In Leszek Szablewski (Ed.), *Blood Glucose Levels*. IntechOpen.

Pettus, J. H., et al., (2019). Incidences of Severe Hypoglycemia and Diabetic Ketoacidosis and Prevalence of Microvascular Complications Stratified by Age and Glycemic Control in US Adult Patients with Type 1 Diabetes: A Real-World Study. *Diabetes Care, 42*(12), 2220-2227.

Polit, D. F., & Hungler, B. P., (2013). *Essentials of Nursing Research: Methods, Appraisal, and Utilization* (8th Ed.). Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins.

Rajasekar, S. P., Philominathan, P., & Chinnathambi, V., (2013). Research Methodology. arXiv: physics/0601009v3 [physics.gen-ph]

Shubrook, J. H., (2020). Recognition and Management of Hypoglycemia. *Supplement to the Journal of Family Practice, 69*(7), S63-S68.

Tenzer-Iglesias, P., et al., (2012). Managing Hypoglycemia in Primary Care. *Supplement to the Journal of Family Practice, 61*(10), S1-S8.

van Dalem, J., et al., (2016). Risk of Hypoglycaemia in Users of Sulphonylureas Compared with Metformin in Relation to Renal Function and Sulphonylurea Metabolite Group: Population Based Cohort Study. *BMJ*, 354, i3625.

Whipple, A. O., (1938). The Surgical Therapy of Hyperinsulinism. *Journal International de Chirurgie, 3*, 237-276.