DIABETES AND METABOLIC DISORDERS CONTINUING EDUCATION REVIEW

415 Essay Questions
and Referenced Answers

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Diabetes and Metabolic Disorders

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415 ESSAY QUESTIONS AND REFERENCED ANSWERS

by

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Preface

Advances in our understanding of diabetes mellitus and other metabolic disorders have proceeded at an accelerated pace over the past decade. The development of new, sophisticated techniques for study, such as hormone radioimmunoassay, electron microscopy, and automated clinical chemistry analysis, has brought increased knowledge of common diseases, as well as new recognition and understanding of unusual disorders of metabolism.

It is the purpose of the present book to provide an overview of these recent developments in diabetes mellitus and other metabolic disorders. An essay question and answer technique is used, and references are cited for the key articles which consider each subject. Material is approximately equally divided between diabetes mellitus and the other metabolic disorders.

While not encyclopedic in its scope, this volume is designed to cover important advances in metabolism in recent years, and considers such diverse areas as pathophysiology of diabetes, diabetic vascular diseases and comas, treatment of diabetes, genetics and vitamins, lipid and mineral metabolism, connective tissue disorders, hypoglycemia, and glycogen storage diseases. It is hoped that this review will serve as a reminder of recent advances and as an impetus to the reader to consult the original source material when needed to improve his own understanding of diabetes mellitus and metabolic disorders.

The authors would like to express their thanks for the expert administrative assistance of Cornelia Campbell, the secretarial help of Donna Dix, and the medical library assistance of Jane Crane.

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PART ONE. DIABETES MELLITUS

I. PATHOPHYSIOLOGY OF DIABETES

1. Q. What is the precursor of insulin in the β cell?

A. Insulin is derived from a precursor molecule, proinsulin, which is synthesized in the endoplasmic reticulum. The site at which the C-peptide portion of the proinsulin molecule is split off giving rise to insulin has not been definitely established but appears to take place in the Golgi complex.
REF. Lacy PE, et al.: New hypothesis of insulin secretion. Nature (London) 219:1177-1179, 1968.

2. Q. What is the storage form of insulin?

A. The insulin molecule is stored in granular form (the beta granule) as a zinc insulin complex which has a crystalline structure.
REF. Lacy PE, et al.: New hypothesis on insulin secretion. Nature (London) 219:1177-1179, 1968.

3. Q. Describe the morphologic events in the β cell which occur with insulin secretion.

A. The release of insulin from the beta cell is accomplished by movement of the β granule in its sac to the cell surface where the membrane of the sac fuses with the plasma membrane. The fused membranes then rupture, releasing the contents of the sac to the extracellular space.
REF. Lacy PE, et al.: New hypothesis of insulin secretion. Nature (London) 219:1177-1179, 1968.

4. Q. What is the role of the microtubular systems of the β cell in insulin secretion?

A. In recent years, a great deal of interest has been focused on the possibility that the microtubular-microfilament system may play an important role in the "mechanics" of insulin secretion. It has been suggested that the beta granules are in some way associated with the microtubules and that contraction of the latter facilitates movement of the granules to the cell surface and their subsequent release.
REF. Lacy PE, et al.: New hypothesis on insulin secretion. Nature (London) 219:1177-1179, 1968.

5. Q. In vitro what is the minimal glucose threshold for insulin release, and the maximal glucose concentration at which secretion becomes stable?

A. The minimal concentration is 50 mg%; secretion becomes maximal at 300 mg%.
REF. Grodsky GM.: Insulin and the pancreas. Vitam. Horm. 28:37, 1970.

6. Q. What is the role of calcium in insulin secretion?

A. Glucose-stimulated insulin release is associated with increased calcium accumulation within the β cell which may activate the microtubular-microfilament system.
REF. Malaisse WJ. : Insulin secretion:multifactorial regulation for a single process of release. Diabetologia 9:167-173, 1973.

7. Q. Describe the two phases of insulin secretion.

A. There is an immediate, first phase, of insulin secretion followed by a second late phase when a constant glucose stimulus is used.
REF. Grodsky GM. : Insulin and the pancreas. Vitam. Horm. 28:37, 1970.

8. Q. List the three physiologic regulators of insulin secretion.

A. 1. Nutrients: glucose, amino acids, fatty acids
2. Gastric and GI hormones: glucagon, pancreozymin, etc.
3. Nervous system: catecholamines, vagus nerve
REF. Malaisse WJ. : Insulin secretion:multifactorial regulation for a single process of release. Diabetologia 9:167, 1973.

9. Q. Describe the clinical importance of the following sequence of biochemical reactions.

$$\text{Alanine} \longrightarrow \text{Pyruvate} \xrightarrow{+CO_2} \text{Oxaloacetate} \xrightarrow{+GTP} \text{Phosphoenolpyruvate}$$

A. The amino acid alanine is utilized as the donor of the carbon skeleton of pyruvate. Under conditions of increased need for glucose production, this reaction initiates the flow of substrate through the gluconeogenic pathway. Other amino acids except leucine may also be used as substrates for glucose production by the liver.
REF. Coleman JE. : Metabolic interrelationship between carbohydrates, lipids and proteins. Bondy PK, Felig P. : Disorders of carbohydrate metabolism. Bondy PK, Rosenberg LE, (Eds.). : Duncan's diseases of metabolism, W. B. Saunders Company, Philadelphia-London-Toronto, 1974, pp. 221-340B.

10. Q. Proinsulin is cleaved into what two peptides?

A. 1. Insulin
2. C-peptide
REF. Steiner DF, et al. : The biosynthesis of insulin. Steiner DF, Freinkel N, (Eds.). : Handbook of physiology - endocrinology I, Williams and Wilkins Co. . Baltimore, Maryland, Chapter 10, pp. 175-198, 1972.

11. Q. Where is C-peptide stored?

A. Within the β cell. It is secreted together with insulin and may serve as a good marker of insulin reserve in situations where immunoassays of insulin cannot be done (i.e., in patients who have been on long-term insulin therapy, where insulin antibodies interfere with the assay).
REF. Rubenstein A, et al.: Proinsulin and C-peptide in blood. Diabetes 21 (Supplement 2):673, 1972.

12. Q. Is there a good correlation between C-peptide and insulin levels in plasma of normal subjects after glucose loading?

A. Yes. Studies by Block et al have shown a clear correlation, suggesting that C-peptide and insulin are secreted together.
REF. Block MB, et al.: Circulating C-peptide immunoreactivity: studies in normals and diabetic patients. Diabetes 21:1013-1026, 1972.

13. Q. Give two effects of insulin on the cell membrane of responsive tissues.

A. 1. Alter membrane permeability after fixation on receptor site.
2. Accelerate carrier-mediated transport of sugars and amino acids, particularly in muscle and fat.
REF. Cahill GF, Jr.: Physiology of insulin in man. Diabetes 20:785-799, 1971.

14. Q. What are the two tissues which are primarily responsive to insulin?

A. Adipose - glucose uptake, fat synthesis, fat uptake, decreased lipolysis. Muscle - glucose uptake, amino acid uptake, protein synthesis, decreased proteolysis.
REF. Cahill GF, Jr.: Physiology of insulin in man. Diabetes 20:785-799, 1971.

15. Q. In tissues such as fat and muscle, does glucose entry occur via passive diffusion or by some other mechanism?

A. Recent evidence suggests that glucose entry into the cells of adipose and muscle is facilitated by a highly developed membrane transport system. It is the activity of this transport system which is stimulated by insulin. Although a glucose receptor is postulated within the membranes of these cells, one has not yet been characterized.
REF. Park CR, et al.: Mediated (non-active) transport of glucose in mammalian cells and its regulation. Biological interfaces:flows and exchanges. Boston, Little, Brown & Company, 1968, pp. 296-318.

16. Q. List the effects of insulin on the fat cell.

A. 1. Stimulate glucose uptake and lipogenesis
2. Inhibit free fatty acid release through inhibition of hormone sensitive lipase.
3. Maintain normal lipoprotein lipase levels

REF. Avruch J, et al.: The effect of insulin on the metabolism of adipose tissue. Handbook of physiology, Section 7, Vol. 1 Endocrine Pancreas (Steiner DF, Freinkel N, Eds.). American physiological society, Washington, D.C., 1972, p. 545.

17. Q. Is the action of insulin on glucose transport linked to the cyclic AMP system?

A. No. It may be the only peptide hormone which does not exert an action on the cell which is mediated through this system.
REF. Butcher RW, et al.: The role of cyclic AMP in hormone actions. Weber G, (Ed.): Advances in enzyme regulation, Vol. 6. Oxford, Pergamon Press, 1968, pp. 357-389.

18. Q. Give the effects of low insulin concentrations on muscle and adipose tissue.

A. 1. Muscle - proteolysis and amino acid release
2. Adipose - lipolysis and fatty acid release

REF. Cahill GF, Jr.: Physiology of insulin in man. Diabetes 20:785-799, 1971.

19. Q. What quantitative estimates may be made of daily protein and fat breakdown during total fasting in man?

A. 75 gm of muscle, 160 gm of fat during early days of total starvation and 10 gm of muscle and 150 gm of fat after 5-6 weeks of fasting.
REF. Cahill GF, Jr.: Physiology of insulin in man. Diabetes 20: 785-799, 1971.

20. Q. Give a quantitative estimate, in grams per day, of the glucose utilized by the brain, the muscles and the formed elements of the blood and renal medulla.

A. The nervous tissue accounts for the utilization of 125 and 150 grams of glucose per day. An additional 100 grams is extracted by the muscles, the formed elements of the blood and the renal medulla.
REF. Bondy PK, Felig P.: Disorders of carbohydrate metabolism. Bondy PK, Rosenberg LE (Eds.), Duncan's diseases of metabolism, W. B. Saunders Co., Philadelphia-London-Toronto, pp. 221-340B, 1974.

21. Q. Give 3 reasons why the liver assumes a unique role in glucose homeostasis.

A. 1. In the basal state, glucose is continuously released from liver at a rate of 2 to 3.5 mg per kg per minute (200 to 350 gm per day).
2. The membrane of the liver cell is freely permeable to glucose.
3. The level of insulin in portal blood is 5 to 10-fold greater than that in peripheral blood. This portal-peripheral gradient is a consequence of secretion of insulin directly into the portal system and the capacity of the liver to remove 50 to 80 per cent of the insulin reaching it.

REF. Madison LL.: Role of insulin in the hepatic handling of glucose. Arch. Intern. Med. 123:284, 1969.

22. Q. What is the immediate insulin response to intravenous glucose in prediabetes?

A. Recent studies have confirmed older work which showed that the early insulin response (0, 5, 7, and 12 minutes after glucose) is low in siblings of genetic diabetics (71+41 μU/ml) than in controls (116+58 μU/ml). However, the early insulin response is not sufficiently characteristic to classify a patient as a prediabetic.
REF. Sterky G, Thorell JI.: Early insulin response to glucose stimulation in siblings of juvenile diabetics. Acta Endocrinol. 73:721-730, 1973.

23. Q. Give the effects of high and low concentrations of insulin on the liver.

A. 1. High insulin - decreased hepatic glucose output, increased glycogen storage and fat synthesis
2. Low insulin - increased glucose release, glycogenolysis, gluconeogenesis and partial fat oxidation to ketoacids

REF. Cahill GF, Jr.: Physiology of insulin in man. Diabetes 20: 785-799, 1971.

24. Q. With a small increment of insulin secretion induced by glucose infusion, does the liver or the periphery display the main response?

A. The liver. With infusions to raise plasma glucose from about 70 to 90 mg/100ml and insulin from 10 to 20 μU/ml, the major action of insulin is to suppress hepatic glucose output.
REF. Felig P, Wahren J.: Influence of endogenous insulin secretion on splanchnic glucose and amino acid metabolism in man. J. Clin. Invest. 50:1702, 1971.

25. Q. What fraction of an oral glucose load is disposed of in the liver in normal man?

A. Approximately 75% of an oral glucose load is disposed of in the liver.
REF. Felig P, Wahren J. : Influence of endogenous insulin secretion on splanchnic glucose and amino acid metabolism in man. J. Clin. Invest. 50: 1702, 1971.

26. Q. What is the mechanism for normal glucose tolerance in the presence of a diminished early insulin response in prediabetes?

A. An augmented hepatic sensitivity to endogenously secreted insulin.
REF. Wahren J, et al. : Splanchnic glucose production and its regulation in healthy monozygotic twins of diabetics. Clin. Sci. 44:493-504, 1973.

27. Q. What are the major nutrients which contribute to hepatic glucose production through gluconeogenesis in obese patients?

A.	Obese	Normals
Amino Acids	10%	6
Lactate	25%	12
Glycerol	2%	1
"Glycogen"	63%	81

REF. Felig P, Wahren J. : Amino acids and gluconeogenesis: Influence of blood cells, obesity, prolonged exercise and glucocorticoids. Excerpta Medica, Amsterdam, Proc. of the Eighth Congress of the International Diabetes Federation, pp. 217-230, 1974.

28. Q. What are the major organs of glucose uptake in the fasting state?

A. 1. Brain (approximately 144 gm/day)
2. WBC and RBC (36 gm/day)
REF. Cahill GF, Jr. : Physiology of insulin in man. Diabetes 20:785-799, 1971.

29. Q. Which levels are higher after a meal, peripheral or portal venous insulin?

A. Portal. From 1-2 minutes after 25 grams of glucose p.o., portal insulin concentrations are from 5-10 times greater than that in peripheral blood.
REF. Blackard WG, Nelson NC. : Portal and peripheral vein immunoreactive insulin concentrations before and after glucose infusion. Diabetes 19:302-306, 1970.

30. Q. Is there any abnormality of the renal tubular maximum reabsorption capacity for glucose (T_{MG}) in diabetic subjects ?

A. Yes. The T_{MG} is significantly higher in diabetics than in normals. This abnormality is in proportion to the GFR in these

subjects. This partially explains the tendency for some diabetic subjects to show minimal glycosuria at high blood glucose levels.
REF. Mogenson CE. : Maximum tubular reabsorption capacity for glucose and renal hemodynamics during rapid hypertonic glucose infusion in normal and diabetic subjects. Scand. J. Clin. Lab. Invest. 28:101-109, 1971 .

31. Q. What are the major effects of glucagon in physiologic doses?

A. 1. Hepatic actions: stimulates gluconeogenesis and glycogenolysis
2. Extrahepatic actions: stimulation of insulin secretion, elevation of free fatty acids, stimulation of renal electrolyte excretion, inhibition of gastrointestinal motility.
REF. Sokal JE. : Glucagon. Ellenberg M, Rifkin H, (Eds.) Diabetes mellitus: theory and practice, New York, McGraw-Hill Book Co., 1970, pp. 112-131.

32. Q. What sugar pathway may be responsible for alterations in lens, nerve, retina, kidney, blood vessels and islet cells?

A. A conversion of glucose to sorbitol via the enzyme aldose reductase and subsequent conversion of sorbitol to fructose via sorbitol dehydrogenase. These sugar alcohols are formed intracellularly and are poorly metabolized, leading to hypertonicity.
REF. Gabbay KH. : The sorbitol pathway and the complications of diabetes. N. E. J. M. 288:831-836, 1973.

33. Q. How are plasma glucose and insulin concentrations related following meals in normal subjects?

A. In normal subjects, post-prandial plasma glucose concentrations rarely exceed 130 mg/100ml. Within minutes after eating, plasma insulin levels rise to 5-10 times above the basal state. Within 0-2 hours after eating, plasma glucose and insulin return to their basal concentrations.
REF. Hansen A, Johansen K. : Diurnal patterns of blood glucose, serum free fatty acids, insulin, glucagon and growth hormone in normals and juvenile diabetics. Diabetologia 6:27-33, 1970.

34. Q. How are plasma glucose and insulin levels related to meals in ketosis prone diabetic subjects?

A. In these subjects, fasting plasma glucose levels are high (>200 mg/100ml) and insulin levels are low or absent. There is no rise in insulin levels post-prandially. Glucose levels may rise over 300 mg/100ml.
REF. Hansen A, Johansen K. : Diurnal patterns of blood glucose, serum free fatty acids, insulin, glucagon and growth hormone in normals and juvenile diabetics. Diabetologia 6:27-33, 1970.

35. Q. What are the primary abnormalities of circulating hormone and fuel concentrations in labile or brittle diabetes mellitus?

A. 1. Excessive within-day and between-day blood glucose variability
2. High diurnal growth hormone levels
3. Negative correlation of immunoreactive insulin with blood glucose levels.

REF. Molnar GD, et al.: Diurnal growth hormone and glucose abnormalities in unstable diabetics: Studies of ambulatory-fed subjects during continuous blood glucose analysis. J. Clin. Endocrinol. 34: 837-846, 1972.

36. Q. What is the effect of glucose on plasma glucagon levels in diabetes as opposed to normals?

A. Whereas normals show a suppression of plasma glucagon levels with glucose, this does not occur in severe diabetics. The molar ratio between insulin and glucagon is low in severe diabetics; and, its effects to increase blood glucose are apparent.
REF. Unger RH, et al.: Insulin/glucagon ratio. Trans. Assoc. Am. Physicians 84:122, 1971.

37. Q. Describe the role played by the enzymes hexokinase and glucokinase in the liver cells.

A. Both enzymes control the phosphorylation of glucose to glucose-6-phosphate soon after glucose enters the hepatic cell. The difference between them resides in the fact that hexokinase is not specific for glucose and it accepts fructose as a substrate. In addition this enzyme is half saturated at glucose concentration of only 0.18 mg/100ml. Glucokinase on the other hand is half saturated only when the glucose concentration in the medium has risen to 180 mg/100ml and is also more active in catalyzing the phosphorylation of glucose than that of fructose.
REF. Brown J, et al.: Hexokinase isoenzymes in liver and adipose tissue of man. Science 155:205-207, 1967.

II. DIAGNOSIS OF DIABETES

38. Q. Give a definition of diabetes mellitus.

A. Diabetes mellitus is a genetically determined disorder of metabolism associated with relative or absolute insulin insufficiency, which in its fully developed clinical expression is characterized by fasting hyperglycemia, atherosclerotic and microangiopathic vascular disease, and neuropathy.
REF. Fajans SS.: What is diabetes? Definition, diagnosis and course. Med. Clin. North. Am. 55:793-805, 1971.

39. Q. List 5 possible causes of diabetes mellitus.

A. 1. Genetic
2. Stress
3. Autoimmunity
4. Viral infection
5. Microvascular lesions of pancreatic capillaries
REF. Diabetes, Malaisse WJ, Pirart J, (Eds.), Excerpta Medica, Amsterdam, Proc. of the Eighth Congress of the International Diabetes Federation, pp. 3-21, 53-62, 285-326, 346-352, 1974.

40. Q. Is there suggestive evidence that diabetes may be due to a viral infection?

A. Yes. A strain of the encephalomyocarditis virus will produce insular lesions and diabetes in mice. This virus is a picornavirus, to which group belong poliovirus, coxsackie A and B, echo virus, and rhinovirus. However, no virus has yet been cultured from blood or pancreatic tissue in diabetic humans suspected to have viral-induced diabetes.
REF. Steinke J, Taylor KW.: Viruses and the etiology of diabetes. Diabetes 23:631-633, 1974.

41. Q. What is a type of autoimmune syndrome associated with diabetes mellitus?

A. Schmidt's Syndrome. This syndrome consists of thyroid, adrenal, and pancreatic beta cell deficiency resulting in hypothyroidism, adrenal insufficiency and diabetes mellitus. It is quite rare.
REF. Carpenter CCJ, et al.: Schmidt's Syndrome (thyroid and adrenal insufficiency). A review of the literature and a report of fifteen new cases including ten instances of coexistent diabetes mellitus. Medicine 43:153, 1964.

42. Q. What are the criteria for the diagnosis of diabetes mellitus in adults using the Fajans-Conn technique of glucose tolerance testing?

A. The glucose load may be either 100 gm or 1. 75 gm/Kg of desirable body weight (Metropolitan Life Insurance table for adults with medium frame). Glucose is determined by the Auto Analyzer method on venous plasma or whole blood. In otherwise healthy and ambulatory individuals under age fifty, a diagnosis of diabetes is made if all three of the following values are equal to or greater than those shown:

	mg/100ml	
Time	Plasma or Serum	Whole Blood
One hour	185	160
1 1/2 hours	160	140
2 hours	140	120

REF. Fajans SS, Conn JW. : The early recognition of diabetes mellitus. Ann. N.Y. Acad. Sci. 82:208-218, 1959.

43. Q. Using the Wilkerson (USPHS) point system, what are the criteria for the diagnosis of diabetes mellitus by oral glucose tolerance testing?

A. Using a 100 gm glucose load and venous plasma or whole blood samples, the glucose values as determined by the Somogyi-Nelson method are weighed as follows:

	(mg/100ml)		
Time	Plasma or Serum	Whole Blood	Points
Fasting	125	110	1
1 hour	195	170	1/2
2 hours	140	120	1/2
3 hours	125	110	1

Points are given as shown if values exceed those listed. A total of two points or more is diagnostic of diabetes.
REF. O'Sullivan JB. : Oral glucose tolerance tests. Hamwi GJ, Danowski TS, (Eds.), Diabetes Mellitus: Diagnosis and Treatment Vol. II, New York, American Diabetes Association, Inc., June, 1967, pp. 47-50.

44. Q. What are the accepted criteria for the diagnosis of diabetes in children by oral glucose tolerance testing?

A. After an overnight fast of 10 hours, an oral glucose load of 1. 75 gm/Kg of ideal body weight is given. Glucose is determined by either the Auto Analyzer or Somogyi-Nelson method either on capillary whole blood (= arterial glucose level) or on venous plasma. If two or more values on a single test are higher than the following criteria, a tentative diagnosis of chemical diabetes is made. This should be substantiated by repeat testing.

	(mg/100ml)	
Time	Capillary Whole Blood	Venous Plasma
Fasting	110	110
1 hour	170	160
2 hours	140	140
3 hours	125	130
4 hours	110	115