Translational Research Methods in Diabetes, Obesity, and Nonalcoholic Fatty Liver Disease

A Focus on Early Phase Clinical Drug Development

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Editors

Second Edition

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Foreword

Obesity, type 2 diabetes, and associated metabolic diseases such as nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), have reached epidemic proportions on a global scale. Insulin resistance is a fundamental etiologic defect in type 2 diabetes, and obesity is the most common cause of insulin resistance in man. There is a great deal of phenotypic overlap between obesity, type 2 diabetes, and NAFLD/NASH, and the great majority of patients who ultimately develop NASH are obese and insulin resistant. Taken together, these disorders represent one of the greatest areas of unmet medical need, creating the opportunity to discover and test new potential drugs. The chapters in this book provide an important contribution to our knowledge on the scientific and regulatory issues related to preclinical studies, with a major emphasis on the early stages of clinical development. As such, the material in this book includes a discussion of the latest methodologies in metabolic research, focusing on early clinical proof of mechanism, early-stage indicators of drug efficacy, biomarkers, and safety. In today's landscape of drug development, a major goal is to collect information allowing the quickest possible decision on whether a drug candidate operates through the expected mechanism with the desired pharmaceutical properties of target engagement, pharmacokinetics, safety, and the necessary degree of efficacy. Hopefully, this allows informed go/no-go decisions, which enable biopharmaceutical companies to intensify their efforts on the most promising drug candidates.

In this second edition of the book, the spectrum of NAFLD/NASH/cirrhosis garners much attention since this is a very active area of metabolic disease drug discovery and development, with many active clinical programs. By using the most cutting-edge in vivo methodologies to assess insulin sensitivity, insulin secretion, thermogenesis, and metabolomics, much can be learned in the early stages of clinical development which has not been possible in the past. In addition, modern imaging techniques allow assessments of hepatic fat content and liver elasticity, providing noninvasive measures across the spectrum of NAFLD/NASH. With all of these approaches available, carefully designed proof of mechanism studies will allow earlier and cleaner decisions on development programs, making resource allocations far more efficient and informative.

The editors of this book, Andrew Krentz, Christian Weyer, and Marcus Hompesch, are all highly experienced experts in academic research and drug

development. They have recruited an expanded list of world leaders in metabolic research to cover a wider range of topics for this second edition.

The new edition of the textbook retains the division into two main sections: the first section presents an even more comprehensive review of clinical investigative techniques used in early-phase clinical drug development for diabetes and NAFLD/NASH. This section employs a structured approach that was successfully pioneered in the first edition. Notable new chapters in this section include the assessment of islet α- and β-cell function, the quantification of appetite and satiety, and the role of tissue biopsy in drug development. Imaging of NAFLD/NASH and other disorders characterized by ectopic fat deposition has been updated, and a new chapter covers state-of--the-art functional imaging of key organs including muscle, heart, pancreas, and kidneys.

The second section expands the perspective to preclinical drug development and transitioning to clinical studies. Included in this section are new chapters on drug design focusing on peptide drugs, biomarkers for NAFLD/NASH, and clinical trial endpoints that lie beyond reducing glycated hemoglobin concentrations. The chapter on regulatory considerations has been expanded with a new emphasis on emerging therapies for NAFLD/NASH.

The audience for this textbook includes scientists and clinicians in the biopharmaceutical industry involved in the design and implementation of first-in-man proof of mechanism and efficacy studies. Academic scientists engaged in metabolic research will also find this book to be an important resource. Lastly, this book will be beneficial to a broader audience including students and fellows who are at the early stages of their careers in this field.

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Preface

We are very pleased to present the second edition of this textbook.

The positive reception to the first edition was most gratifying for the authors and editors. The popularity of the textbook provided support for the view that we had achieved our objective of providing a useful guide for investigators involved in early-phase drug development for diabetes, obesity, and related disorders.

In this second edition, we are expanding the scope by placing further emphasis on the spectrum of nonalcoholic fatty liver disease (NAFLD). This decision reflects the increasing global impact of this highly prevalent disorder, its serious health implications, and the present unmet need for the development of effective pharmacotherapies. These considerations are currently driving an intense drug development effort aimed primarily at the clinically important subtype of nonalcoholic steatohepatitis (NASH) which carries an increased risk of fibrosis, cirrhosis, and hepatocellular carcinoma. Relevant new chapters in the second edition cover invasive (liver biopsy) and emerging noninvasive imaging and circulating diagnostic and pharmacodynamic biomarkers for NAFLD/NASH.

Other new additions include cardiovascular research methodologies, assessment of appetite and satiety, and transitioning from preclinical to clinical research. Furthermore, every chapter that appeared in the first edition has been revised and updated based on scientific advances in the field.

The focus of the first part of the book remains on the selection of the most appropriate means of achieving the key objectives of early-phase drug development trials. The pros and cons of established and emerging clinical research methodologies are carefully considered and presented in a balanced and accessible format.

The remainder of the book covers topics that include biomarkers for diabetes and insulin resistance, aspects of drug design for diabetes and related metabolic diseases, quantitative approaches to drug safety and efficacy, regulatory considerations, and the challenges of identifying appropriate subjects for clinical trials. The concepts of personalized and precision medicine are well represented throughout the book.

It has been our pleasure and honor to work with the distinguished authors who have made important contributions in bringing this second edition to fruition. We are immensely grateful for the time and effort that the authors – all acknowledged leaders in their fields – have invested. The shared objective

to create a state-of-the-art textbook of value to clinicians and scientists has been evident at all stages.

We also thank Melissa Morton, Prakash Jagannathan, and their colleagues at Springer for the support and encouragement.

Feedback from readers that will help inform future editions of the book is most welcome.

Chula Vista, CA, USA — Andrew J.Krentz
Christian Weyer
March 2019 — Marcus Hompesch

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Part I

Review of Clinical Investigative Methods

1 Quantification of Insulin Action in Human Subjects

Andrew J. Krentz, Christian Weyer, and Marcus Hompesch

Summary

Background

Insulin resistance is a characteristic pathological hallmark of obesity, type 2 diabetes and nonalcoholic fatty liver disease. Reducing adiposity through non-pharmacological or pharmacological interventions improves whole-body insulin sensitivity. As an adjunct to lifestyle measures, insulin-sensitizing drugs, such as thiazolidinediones and the biguanide metformin, have a well-established role in the treatment of type 2 diabetes. In the context of drug development, insulin action is primarily focused on the assessment of whole-body glucose metabolism. Additional considerations include the contribution of major organ systems, i.e., liver, adipose tissue, muscle, brain, and the regulation by insulin of lipid, protein and amino acid metabolism. Improving insulin sensitivity with thiazolidinediones improves glycemic control and may have protective effects on the cardiovascular system. However, unwanted effects include weight gain, fluid retention and an increased risk of fractures.

Key Methods

Accurate and reproducible measurement of insulin sensitivity is required to evaluate new drugs with insulin-sensitizing properties. Methods for quantifying insulin action may be usefully classified according to whether the physiological feedback loop between the islet β-cells and insulin-sensitive target tissues is maintained (closed-loop) or interrupted through pharmacological manipulation (open-loop).

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(a) Closed-loop methods

	Method	Measure	Advantages	Disadvantages	Value in drug development decisions
Fasting serum insulin and glucose; mathematic models include HOMA[a], HOMA2, iHOMA2 and QUICKI[b]	Venous serum insulin and plasma glucose are measured in blood samples drawn after an 8–12 h overnight fast	Insulin sensitivity (%S)	Technically simple; relatively inexpensive; provides an indication of insulin sensitivity in the basal state	Indirect assessment of insulin action; only assesses metabolism in basal (non-stimulated) state; degree of insulin resistance may be underestimated in the presence of hyperglycemia	May provide useful exploratory data in early phase studies; results should be confirmed with a dynamic test of insulin sensitivity; iHOMA2 permits modelling of physiology and drug treatment effects
Mixed meal tolerance test (MMTT)	Plasma glucose and serum insulin responses at defined intervals to a standardized meal	Area under the curve (AUC) for insulin; mathematical models of insulin and glucose responses (e.g. Matsuda Index; Stumvoll Index)	Provides data of relevance to human physiology; flexible, i.e. nutrient components can be adjusted; assesses integrity of incretin axis	Indirect assessment of insulin action; issues of intra-individual and between-individual variability; may be affected by gastric emptying rate	May be of value in providing early signal of effects of drugs on insulin action
Oral glucose tolerance test (OGTT)	Glucose, insulin and/or C-peptide responses to 75 g oral glucose	AUC for insulin; mathematical models of insulin and glucose responses	Simple to perform; reference methods for diagnosing diabetes and impaired glucose tolerance; large existing scientific literature	Indirect assessment of insulin action; issues of intra-subject and inter-subject variability; β-cell response to secretagogues other than glucose is not assessed; may be affected by gastric emptying rate	May be of value in providing early signal of effects of drugs on insulin action
Insulin tolerance test (ITT)	Response of blood glucose to an intravenous bolus of glucose	Glucose disposal rate (K_{ITT})	Technically straightforward	Risk of hypoglycemia; cannot partition insulin action between insulin-mediated glucose disposal and suppression of hepatic glucose production	Limited role in diabetes drug development

[a]Homeostasis model assessment
[b]Quantitative insulin sensitivity check

(b) Open-loop methods

	Somatostatin is infused to suppress endogenous insulin secretion; exogenous insulin and glucose are infused intravenously to achieve steady-state plasma glucose	Steady-state plasma glucose (SSPG)	Reproducible steady-state method which eliminates endogenous insulin secretion and assesses insulin-mediated glucose disposal	Indirect assessment of insulin action on glucose metabolism; labour intensive; relatively inflexible; hepatic insulin sensitivity cannot be determined	Limited role in diabetes drug development decisions
Frequently sampled intravenous glucose tolerance test (FSIVGTT)	Glucose, insulin and C-peptide responses to an intravenous bolus of glucose; minimal model analysis of data	Minimal model yields insulin sensitivity index (S_I) and glucose effectiveness (S_G)	Provides dynamic data; widely used in clinical metabolic research	Indirect integrated assessment of glucose metabolism; questionable relevance to physiology	Limited value in diabetes drug development decisions
Insulin sensitivity clamp (two-step euglycaemic hyperinsulinaemic clamp)	Insulin is infused to provide steady-state hyperinsulinemia at pre-determined insulin concentrations; variable rate hypertonic glucose is infused to maintain euglycemia	Glucose disposal rate (M); M/I; Insulin sensitivity index(SI_{clamp})	Direct measure of insulin-mediated glucose disposal; reproducible; low co-efficient of variation; can be combined with complementary techniques, e.g. isotopic determination of glucose turnover, indirect calorimetry; automatic clamps using the Biostator or equivalent devices offer certain advantages over manual clamps	Labour intensive; requires skilled technical staff	Generally regarded as the reference method for determining insulin sensitivity

Conclusions

In the context of early phase drug development of diabetes drugs with insulin-sensitizing properties, selection of the most appropriate method for determining insulin action will be influenced by considerations including putative mechanism of action of the investigational product, budgetary considerations, and expertise of the clinical investigators. Careful selection of study subjects and standardization of dietary intake and physical activity are important considerations in study design. Whole-body insulin sensitivity – which is a composite of hepatic and peripheral insulin sensitivity – is most robustly measured by experienced investigators using the euglycaemic hyperinsulinaemic clamp technique. Advantages of the euglycaemic hyperinsulinaemic clamp include its sensitivity, reproducibility and adaptability. The technique can be readily combined with com-