Clinical Trial Know-How

WHITEPAPER

Clinical Trials in Diabetic Patients - What You Always Wanted to Know, But Never Dared to Ask!

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Clinical Trials in Diabetic Patients

What You Always Wanted to Know, But Never Dared to Ask!

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Diabetes is a serious chronic disease and one of the largest global health emergencies of the 21st century. Due to the risks associated with a raised blood glucose level, each type of diabetes can lead to serious complications in the heart, blood vessels, kidneys, eyes and nerves. The number of cases has steadily increased over the past few decades and has imposed a large economic burden on the global health care system. Thus, there is only one conclusion - it is important to halt the rise of diabetes and improve lives of those affected by conducting research in this area. This paper details the key points to consider when conducting a study on diabetes patients.

Main Types of Diabetes

Besides gestational diabetes, there are two main types of diabetes, type 1 diabetes and the type 2 diabetes. What both types have in common is high blood glucose levels because of the body not producing enough insulin or not responding properly to insulin.

Type 1 diabetes is caused by an autoimmune reaction, whereby the body´s defense system attacks the insulin producing beta cells in the pancreas. The cause of this reaction is not fully understood. The onset usually occurs in children or young adults and accounts for about 5% of all cases of diabetes. These people need insulin every day to control the blood glucose values. Without insulin, a person with type 1 diabetes cannot survive.

Type 2 diabetes is the most prevalent form with up to 91% of adults in high-income countries. It usually occurs in adults, but it´s also seen in children and adolescents. Initially, the body is able to produce insulin, but becomes resistant so that the insulin is ineffective. By and by insulin levels may subsequently become insufficient. At the beginning many people with type 2 diabetes are unaware of their illness as symptoms like excessive thirst, frequent urination, weight loss and blurred vision are less marked than in type 1 diabetes. During this time, elevated blood glucose can damage the body and the patient can start to have complications. The exact cause for the development of this form of diabetes is still unknown, but there are some important risk factors such as high body weight, physical inactivity, poor nutrition, family history of diabetes, gestational diabetes and advancing age.

Diabetes: A Global Emergency

According to the seventh edition of the Diabetes-Atlas of the International Diabetes Federation (IDF), published with data collected in 2015, it is estimated there are now 415 million adults aged 20 - 79 with diabetes worldwide (1 of 11 adults). An additional 318 million adults are estimated to have impaired glucose tolerance, which puts them at high risk

of developing the disease. Also the trend towards more children developing type 1 diabetes has continued and the number of children with type 1 diabetes has exceeded half a million worldwide.

Each edition of the IDF Diabetes Atlas has shown an increase in the number of people with the disease.

If this rise is not slowed, by 2040 there will be 642 million people (1 of 10 adults) living with the disease. Healthcare costs continue to increase dedicated to diabetes treatment and related complications due to poorly managed diabetes like cardiovascular diseases, blindness, renal failure and amputations. All this shows that diabetes is one of the largest global health emergencies of the 21st century.

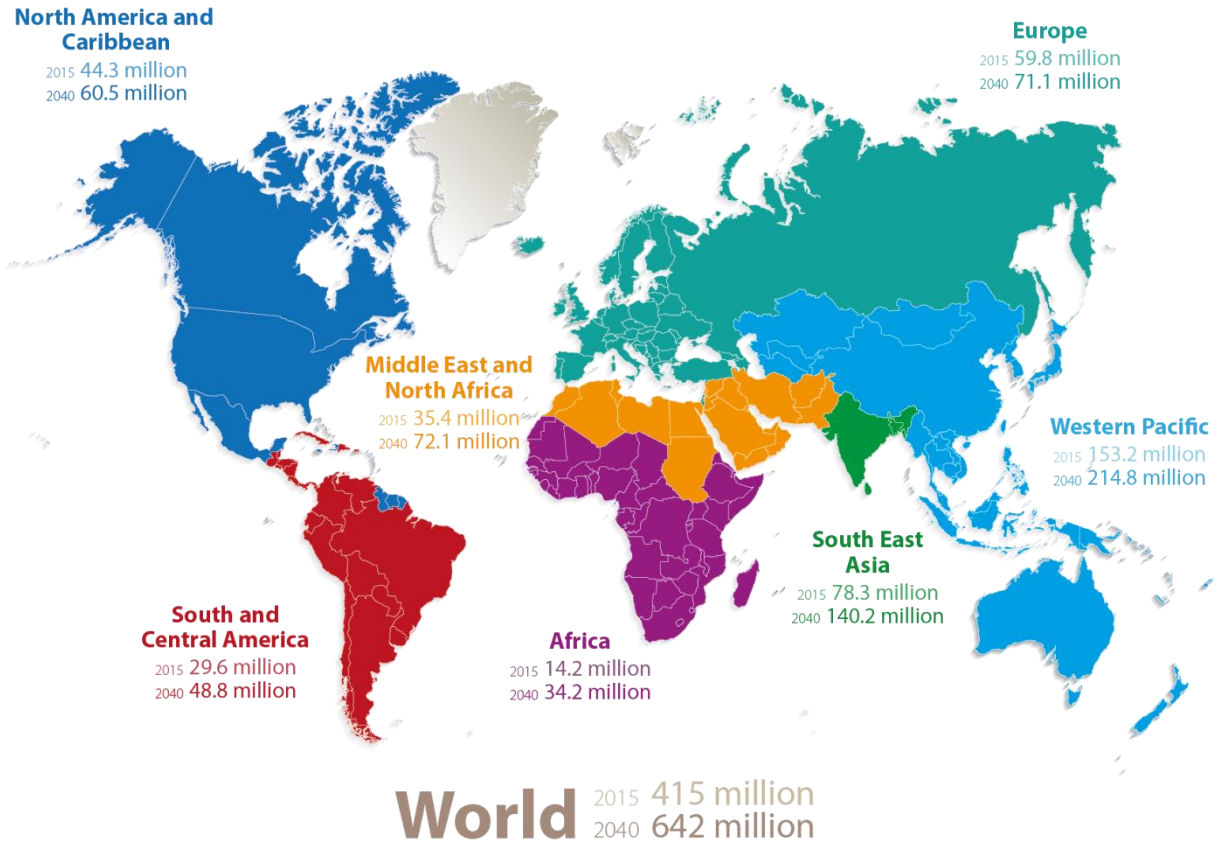

Figure 1: Estimated number of people with diabetes worldwide and per region in 2015 and 2040 (20-79 years). Source: IDF Diabetes Atlas, Seventh Edition 2015 - http://www.diabetesatlas.org/resources/2015-atlas.html

There is only one conclusion - it is important to conduct research in this area of medicine. The goal is the development of individualized strategies, which promoted the early detection of the risk of diabetes and prevention of the disease and its consequences. Furthermore, tailor-made causal therapies are to be developed, which can stop the disease progression and lead to an improvement in patient care. To achieve this goal, diabetes patients can help by participating in a study.

Points to Consider When Performing a Study in Diabetes Patients

Patient recruitment is one major challenge and is crucial for the success of any clinical study. Patients join studies for various reasons that are often determined by the stage of their disease. Some patients who are beginning monotherapy or insulin are often interested in accessing free medicine, information from experts and additional education about their condition. Others are interested in the early intervention to slow progression.

Knowing what motivates patients to participate in a study will facilitate the recruitment of patients who will comply with the study protocol. Two of the key inclusion criteria for diabetes studies are fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c), which gives an indication of average glycaemia over the past 2 or 3 months.

"Knowing what motivates patients to participate in a study will facilitate recruitment"

Only standardized, quality assured laboratory methods may be applied when these values are measured. Per the recommendations of the German Diabetes Association (DDG), the measurement of glucose in venous plasma can only be accurate if glycolysis is inhibited in the blood sample when it is drawn, for example by appropriate additives like citrate plus fluoride. To avoid high screening failure rates, it´s useful to acquire current FPG and HbA1c values from the patient's doctor or the CROs subject database. It is also important to only invite patients who meet protocol requirements to the screening.

After screening, eligible patients often enter a run-in phase of 4 weeks or more. This phase acts as a starting point for the treatment phase with the drug to be tested (e.g. a forced titration of insulin to obtain a fasting plasma glucose target e.g. between 80 mg/dL (4.4. mmol/L) and 100 mg/dL (5.6 mmol/L)).

All patients will be provided with a plasma glucose meter, the corresponding supplies, lancets, test strips and diaries. They will be trained on the self-monitored plasma glucose (SMPG) technique as well as on how to complete the diaries. Training should be repeated as often as necessary.

To reduce errors and minimize attrition, everyone involved in the project must be informed of their intended role at the beginning of the study. It is important that everyone understands how to collect the data, and why accuracy in collecting data is vital to the success of the trial.

When speaking to patients, investigators should convey clear and consistent messaging about the commitment they have made to the study and how inaccurate data collection or dropping out would impact their safety, the accuracy of the results and ultimately the success of the study. An emergency number must be provided to patients for around the clock care.

For trust and compliance, it is important to ensure that the patient can call the facility regardless of the time to clarify uncertainty related to the study. By responding to participants' confusion, the incidence of invalid data can be limited.

The distributed glucose meters should be calibrated in the presence of the patients per instructions in the package leaflet. For data validity, they should also be checked with control solutions regularly. When measuring plasma glucose with test strips, it is important to do everything right. Even patients who have had years (or decades) of experience are not immune to unintentional mistakes which can distort the meaningfulness of the values.

"When measuring plasma glucose with test strips, it is important to do everything right"

It is important to retrain the patients in detail and to point out the sources of error. Possible sources of error include: damp or dirty tests due to not being stored in the original packaging, strips that are not stored between 10 and 30 degrees in a shady area, being placed in the refrigerator, a damp bathroom, or the patient has forgotten to wash his hands before taking the plasma glucose measurement. Even the smallest sugar residue on the fingers, such as residue from an apple eaten the evening before or soap residue can unintentionally elevate levels.

The best practice is to wash hands with warm water to stimulate blood circulation and to dry well, as water can dilute the blood sample. Cream should not be used immediately before the measurement as the measurement result can be corrupted. Disinfection of the fingers is unnecessary, especially since traces of disinfectants can also lead to false values. The fingertip should not be pressed too firmly as the blood sample will be diluted by tissue water and lowered values will be measured. To achieve consistent and valid measurements during a study, it is recommended to guide the patient to carry out the fasting SMPG directly after getting up and before any medication intake or insulin injection.

In addition to sections for recording time and values of fasting SMPG and the corresponding time of breakfast, the patient diary should include sections for recording the time of the start of meals and 7-point SMPG measurements and the time and dose of blood glucose medication intake / insulin injections and Investigational Medicinal Product (IMP) intake / injection during the treatment period.

Hypoglycemia can be a dangerous condition so the signs and symptoms suggesting the occurrence of hypoglycemia as well as the treatment should be listed. Common warning signs of the onset of hypoglycemia are e.g. headache, hunger, rapid heartbeat, trembling, concentration weakness. Signs of an advanced hypoglycemia include aggressiveness. The symptoms of hypoglycemia may also be in normal blood glucose values. This is the case when diabetics have a high blood glucose level for several years because the sugar disease was not detected in time. The body has become accustomed to the constantly increased blood glucose levels, so that normal values are perceived as too low and trigger symptoms of hypoglycemia. Whenever the patient feels hypoglycemic symptoms, plasma glucose should preferably be measured prior to carbohydrate intake to make sure that it is really hypoglycemia. Details on hypoglycemic episodes should be captured and patients should be able to contact the study center as soon as possible to review the details and to decide on any necessary measures as severe hypoglycemia may also lead to seizure or unconsciousness. An injectable form of glucagon as rescue medication should be handed out to patient at the beginning of the study. The patient must be trained by staff and should instruct people who are in frequent contact with them (e.g. family members, coworkers) on how to administer glucagon to treat severe hypoglycemic events if the patient is no longer able to do so.

At the end of the run-in period, mostly during an in-house period, the baseline parameter of the objectives of the study will be collected, e.g. HbA1c, mean of daily fasting SMPG, 7-point-SMPG, post-prandial C-peptide, glucagon and appetite perceptions after a standardized meal, gastric emptying after a standardized labelled test breakfast, etc. This data will be collected again at the end of the treatment phase and compared to assess the effect of the IMP.

One parameter which is consistently correlated with fasting SMPG is the 7-point SMPG profile (7 values: pre-prandial and two hours postprandial for breakfast, lunch, dinner and at bedtime at approximately same time). Two hours postprandial should be defined as two hours after the start of a meal. For any standardized food, it is important to be truly standardized. Everyone must strictly adhere to the gram information of the ingredients.

“One parameter which is consistently correlated with the fasting SMPG is the 7-point SMPG profile”

If it is a multicenter study, the products should be supplied by the same manufacturer. For measuring appetite perceptions as hunger, desire to eat, satiety, etc. a visual analogue scale (VAS) can be used. This is a measurement instrument for subjective sensations that cannot be directly measured.

When responding to a VAS item, respondents specify their level of sensation by indicating a position along a continuous line between two end-points, the most positive and the most negative rating.

The assessment has to be performed alone without any influence of the clinical site or others. For gastric emptying, assessment stable isotope breath testing can be used. (^{13}C)-octanoic acid will be mixed with egg powder and eaten as standardized breakfast. Correct preparation is mandatory. All breath samples are collected in sealable bags. The enrichment of ^{13}C in breath air along the time reflects the velocity of gastric emptying.

Patients who meet all inclusion criteria and none of the exclusion criteria will enter the treatment phase of the clinical investigation and will receive the IMP for the first time. After a review of all safety data they will be discharged, supplied with the appropriate amount of medication until the next visit. It is important to remind the patient to always administer the IMP at the same time and if necessary, at a certain time in relation to a meal. It is also important to return all medication when attending the next on-site visit regardless of whether medication packages are empty or not to check compliance. Regular intermediate telephone communication should be foreseen when planning the study to check any issue with the patients, e.g. values of fasting SMPG, adverse events, etc. At every on-site visit, all SMPG values should be downloaded from the glucose meter. The information recorded into diary should be checked for consistency and be compared with the downloaded SMPG values. This information will help to assess treatment effects and compliance. In the event of inconsistency, the reason must be found and if needed, the patient will need to be trained on correct documentation of the values again.

After the treatment phase and a follow-up period the last visit of the study (EOS) will be performed. Safety parameters will be checked again and post-trial provisions will be taken. A desired highlight of this study is satisfied patients who have had the opportunity to learn new methods to better deal with their illness. If the study results demonstrate that study performance was accurate, a valuable contribution to medical progress has been made.

Only a general outline of the study design features can be given here as the individual design elements and demands of the clinical study protocol depend on the specifications of the mechanism of action and therapeutic target. It is therefore useful to consult an expert for diabetes trials to adequately design and conduct the diabetes trial in a timely and efficient manner. Inamed's medical and regulatory consultants stand at your disposal if you need any help or assistance.

About the Author

Dr. Huber is general practitioner, nutritional physician (KÄB) and a qualified Kneipp physician (KÄB) with more than 20 years of experience in clinical research. For several years, she worked as emergency physician at an emergency ambulance in Munich with more than 750 emergency calls per year. In 1992, she joined the CRO business, where she started working as investigator/principle investigator, site manager and manager of investigators. She conducted phase I (First in Human), phase IIa (proof-of-concept) and phase III clinical trials in several therapeutical areas, which include allergy, cardiology, dyslipidemia, gastroenterology, rheumatology, nephrology and respiratory, and specialized in diabetes research. She was also responsible for the success of large scale nutraceutical studies exceeding 2000 subjects. In 2015, she joined Inamed as an investigator.

About Inamed

For nearly two decades, Inamed has supported the drug and medical device development activities of biotech, pharmaceutical and medical device producing companies through high-quality consulting services, and creating, evaluating and augmenting development concepts. Inamed offers flexible, reliable, high-quality clinical research services, which includes monocenter and multi-center clinical trials with medicinal products from Phase I to Phase IV, including Bioequivalence, Pharmacokinetics, Pharmacodynamics and Proof-of-Concept Trials, as well as clinical investigations with medical devices of Classes IIa, IIb, III and implants in multiple indications. Clinical trial services include study conduct, data management, bio-statistical evaluation and medical writing services. Our successful international experience includes regulatory processes, and proven partnerships with study sites, investigators, CRO partners and academic institutions.

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