



Revista Latinoamericana de Hipertensión

ISSN: 1856-4550

latinoamericanadehipertension@gmail.com

Sociedad Latinoamericana de Hipertensión
Organismo Internacional

Bermúdez, Valmore; Cano, Raquel; Cano, Clímaco; Bermúdez, Fernando; Leal, Elliuz; Acosta, Karen; Mengual, Edgardo; Arraiz, Nailet; Briceño, Carlos; Gómez, Juan; Bustamante, Magaly; Aparicio, Daniel; Cabrera, Mayela; Valdelamar, Lysney; Rodríguez, Moisés; Velasco, Manuel; Israili, Zafar; Hernández, Rafael

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Revista Latinoamericana de Hipertensión, vol. 2, núm. 4, julio-agosto, 2007, pp. 128-134

Sociedad Latinoamericana de Hipertensión
Caracas, Organismo Internacional

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Homeostasis model assessment (HOMA) as surrogate insulinization criteria in patients with type 2 diabetes

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Short Title: HOMA and insulin therapy in Type 2 diabetes

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Recibido 02/05/2007

Aceptado: 10/06/2007

Abstract

Objectives

Type 2 diabetes mellitus is a metabolic disorder that results from defects in both insulin secretion and insulin action. Questions remain about when insulin therapy must be indicated, thus the aim of this study was to evaluate HOMA_{βcell} as surrogate criteria for insulin therapy indication in patients with type 2 diabetes.

Subjects And Methods

A prospective study was performed in 189 type 2 diabetic patients with deficient metabolic control assessed by clinical and laboratory parameters. All patients received nutritional intervention and combination therapy with Metformin and Glimpiride. Patients that did not respond were admitted to the next phase, which consisted in Glimpiride+Metformin+Rosiglitazone oral therapy and then, reevaluated after 3 months. Comparisons between responders and non-responders in this phase were made in order to achieve differences in metabolic parameters and βcell function.

Results

Out of 189 patients studied, 150 (79,36%) were considered as fully responders in the first phase of this study. The remaining 39 patients were admitted in the second trial phase in which 20 patients (51,28%) responded to triple oral therapy, while the other 19 (49,72%) required insulin therapy. Significant differences were found in fasting and post-pandrial glycaemia (p<0,001; p<0,004) between the non-insulin requiring group (200±12,0 mg/dl; 266,05±17,67 mg/dl)

and the insulin-requiring group (291,5±17,6 mg/dl; 361,6±26,1 mg/dl). Likewise, significant differences were observed in HOMA_{IR} and HOMA_{βcell} (p<0,002; p<0,04) between non-insulin requiring patients (7,7±0,8; 24,5±1,3%) vs. insulin-requiring patients (12,6±1,2; 19,4±2,4%). Finally, significant differences were observed when comparing body mass index (non-insulin requiring group 29,2±0,4 Kg/mt² vs. insulin-requiring group 27,1±0,9 Kg/mt²; p<0,05).

Conclusions

HOMA_{βcell} determination in the clinical practice is a useful tool to assess when insulin therapy should be started type 2 diabetic patients.

Key words: HOMA, insulin, type 2 diabetes.

Introduction

According to data published by the World Health Organization (WHO) in 2006, more than 180 million people worldwide have Diabetes and by the year 2030, this number probably will experience a two-fold increase¹. Type 2 Diabetes Mellitus (DM-2) has become a major worldwide public health problem, but is more common in developed countries^{2,3}. By 2025, the countries with the largest number of peo-

ple with DM-2 will be India (> 57 million; prevalence 6%), China (> 37 million; prevalence 3.4%), and the United States (> 21 million; prevalence 8.9%). Currently, over 17 million Americans have been diagnosed with diabetes, and 5.9 million are unaware that they even have the disease. Based on prevalence rates predicted from 1980-1998 trends, the number with diagnosed diabetes in the United States will swell to 29 million by 2050⁴. The increasing incidence of diabetes in developing countries follows the trend of urbanization and "Westernized life style"⁵, suggesting an important environmental effect in interaction with genetic factors responsible for peripheral insulin resistance and secondary β cell dysfunction^{6,7}.

Resistance to peripheral insulin action is due to multiple mechanisms and the intimate molecular basis have been described elegantly by a number of investigators like Randle and more recently by Shulman et al, highlighting that an increase in serum free fatty acids (FFA) are typically associated with insulin-resistant states^{8,9,10}. These compounds compete with glucose for substrate oxidation in muscle cells abolishing insulin-stimulated IRS-1-associated PI 3-kinase activity probably through protein kinase C activation that results in a fall in glucose transport by Glut-4 in muscle cells and adipocytes^{8,11}.

Therapeutic intervention in DM-2 aims β -cell function preservation by direct gluco-lypototoxicity management, peripheral insulin resistance control and rational nutritional approach, allowing a higher glucose uptake in peripheral tissues^{12,13,14,15}. Thus, insulin and secretagogues like sulfonylureas, have been indicated in those patients in whom sensitizing agents monotherapy does not improve overall glucose control^{16,17}. Despite its benefits, the use of these drugs could drive to secondary β -cell exhausting¹⁸. It is estimated that by every year of sulfonylurea treatment 5% of patients present secondary pancreatic failure and thereby lack to obtain a suitable metabolic control regardless of fulfilling nutritional maneuvers, accomplishing physical activity and pharmacological treatment^{19,20}. Pancreatic failure is demonstrated by permanently elevated glucose levels and an increase of advanced glycosylation end products outpost like HbA1c, which make part of the clinical guidelines of insulin therapy in patients with DM-2^{21,22}.

The United Kingdom Prospective Diabetes Study (UKPDS), demonstrated that the percentage of sulfonylurea treatment associated with a secondary response failure (1,395 patients) was of 44% within the 6th year of use with an annual rate of 7.3%²³. By the 10th year of evolution, 70% of type 2 diabetic patients needed treatment with insulin alone or in combination with any of the oral agents²³.

To determine only by clinical parameters accurately when insulin therapy should be required is in most cases difficult in terms of time required to wait in

order to obtain an adequate metabolic response, meanwhile glycosylation, glucotoxicity, lipotoxicity, and atherosclerosis are damaging patient's tissues and organs^{10,15,24}. In most cases, commonly used criteria appear so late in disease evolution that β -cell function is already deeply deteriorated, and thus, functional recovery probabilities are reduced^{21,25}. This fact frequently leads to either unnecessary delayed insulin therapy instauration or precocious therapy with this hormone^{26,27,28,29}.

Since to date there is not a consensus regarding to an optimal timing for insulin treatment initiation (early vs. delayed)^{28,29} and many clinical trials have been carried out by relying on the above mentioned clinical criteria without taking into account the pancreatic secretory reserve^{21,30}, in consequence, the aim of this study was to evaluate pancreatic insulin secretory function in individuals with long-term DM-2 and lack of metabolic control, in order to establish the existence of insulin secretory capacity differences measured through the Homeostasis Model Assessment β -cell (HOMA β -cell)³¹ in patients selected for insulinization by the classical clinical criteria compared to patients under the same clinical circumstances that achieved clinical response with double or triple oral combination therapy (Glymepiride, Metformin, and Rosiglitazone)^{10,28,29,32-34}.

Complicaciones

Subjects and methods

Subjects' selection

A prospective study was performed in which 189 Hispanic whites of both sexes, type 2 diabetic patients diagnosed according to the American Diabetes Association criteria, were included. The patients were recruited from the diabetes consult at the Endocrine and Metabolic Diseases Research Center "Dr. Félix Gómez" (Centro de Investigaciones Endocrino-Metabólicas "Dr. Félix Gómez"), School of Medicine, University of Zulia, Maracaibo, Venezuela.

Patients enrolled in the study were selected according to the following inclusion criteria:

- a) Ages between 40 and 60 years.
- b) Long-term type 2 diabetes (>10 years of evolution since diagnosis).
- c) Long standing lack of metabolic control, despite accomplishing nutritional and pharmacological monotherapy treatment defined by: Hb1Ac > 10 %, fasting glycemia >180 mg/dl and post-pandrial glycemia > 240 mg/dl for more of four consecutive months.
- d) Or patients with previous irregular pharmacological treatment based on sulfonylurea monotherapy or individuals with DM-2 who had never accomplished nor pharmacological or nutritional therapy as treatment and presented metabolic parameters as indicated in A, B and C.
- e) Individuals with previous history of MODY, gesta-

tional diabetes or other pathologies that could cause hyperglycemia (thyroid disease, Cushing's disease, chronic pancreatitis and corticosteroids treatment) were excluded of this study.

Study design

All selected patient underwent fasting and 2 hour venous blood sample collection in order to determine fasting glycemia (glucose-oxidase colorimetric method; HUMAN, Germany) and fasting insulin (solid phase radioimmunoassay, DPC, USA), glycated A1c hemoglobin (HbA1c, cationic exchange resin separation method, SIGMA USA) and post-pandrial glycemia, before pharmacological treatment was administered.

In order to corroborate lack of response to treatment, each patient was submitted to nutritional intervention according to ADA guidelines and to an initial two-drug combination therapy consisting in Metformin (Glucophage, Merck, Germany) 500 – 850 mg with each meal plus Glimepiride (Amaryl, Aventis Pharma, Germany) 2–4mg before breakfast. The follow up period was of 3 months. Patients who reached an euglycemic state defined by fasting and post-pandrial glucose and HbA1c levels normalization were considered as responsive and were not admitted into the next phase of the study. Patients that did not respond were admitted to the next phase, where Rosiglitazone was administered at a dose of 8 mg daily (GlaxoSmithKline, UK) and then, reevaluated after 3 months. Fully responding patients were closely monitored and maintained with a triple oral antidiabetic therapy, and the non-responding patients were placed on insulin therapy at 0,5 – 1 U/kg of body weight per day with weekly adjustments according to basal and postprandial glucose levels.

Comparisons between responding and non-responding patients in the second phase were made in order to achieve differences in the metabolic parameter behavior and β -cell function patterns, previous to final treatment allocation.

Insulin resistance and β -cell functionalism calculation

To derive estimates of β -cell function and insulin resistance, the formulas from the Homeostasis Model Assessment (HOMA) were applied:

- Insulin resistance:

$$\text{HOMA IR} = \frac{\text{Fasting insulin } (\mu\text{U/ml}) \times \text{fasting glucose (mmol/L)}}{22.5}$$

- β -cell function:

$$\text{HOMA } \beta\text{-cell} = \frac{\text{Fasting insulin } (\mu\text{U/ml}) \times 20}{\text{Fasting glucose (mmol/L)} - 3,5}$$

Statistical Analysis

All data was analyzed by SPSS 13.0 for Windows. Normality (or not) variable distribution was assessed by Kolmogorov-Smirnov test. Results were expressed as

arithmetic mean \pm standard error. Differences between means were assessed using unpaired Student's t-test, considering as significant when the value of $p < 0.05$.

Results

Studied patients

Out of 189 patients studied, 150 (79,36%) were considered as fully responders when double oral therapy (Metformin plus Glimepiride) was initiated during the first phase of this study. These individuals achieved and maintained an euglycemic state during all follow-up study period (6 month). The remaining 39 patients were admitted in the second trial phase in order to receive triple oral agent combination (Glymeperide + Metformin + Rosiglitazone), out of which 20 patients (51,28%) responded to therapy, while the remaining 19 (49,72%) required insulin therapy. Overall, 94 % of the patients with clinical insulinization criteria achieved an optimal metabolic control with only nutritional maneuvers, physical activity and dual or triple oral antidiabetic combination therapy.

General data and metabolic parameters in patients admitted to second study phase

Age, evolution time since diagnosis and body mass index

No significant differences were observed between responders and non-responders patients when comparing age (non-insulin requiring group $58,3 \pm 1,9$ years vs. insulin requiring group $54,6 \pm 1,7$ years) and disease evolution since diagnosis (non-insulin requiring group $11,2 \pm 1,5$ years vs. insulin requiring group $11,7 \pm 2,2$ years). A significant difference was observed when comparing body mass index (non-insulin requiring group $29,2 \pm 0,4$ Kg/mt² vs. insulin requiring group $27,2 \pm 1,0$ Kg/mt²; $p < 0,05$). Table 1.

Table 1. Clinic and biochemical patterns in responders and non-responders patients with type-2 diabetes mellitus enrolled in the second study phase

	Responders(n=20)	Non-Responders(n=19)	p
Age	58,4 \pm 1,9	54,6 \pm 1,8	NS
Disease evolution since diagnosis (years)	11,2 \pm 1,5	11,8 \pm 2,3	NS
BMI (kg/m2)	29,2 \pm 0,4	27,2 \pm 1,0	<0,05
Fasting Glycemia (mg/dl)	200,4 \pm 12,0	291,6 \pm 17,6	<0,001
Post-pandrial Glycemia (mg/dl)	266,1 \pm 17,7	361,7 \pm 26,1	<0,004
Fasting Insulin (uU/ml)	15,1 \pm 0,9	17,6 \pm 1,3	NS
Post-pandrial Insulin (uU/ml)	39,6 \pm 1,7	40,2 \pm 3,9	NS
HbA1C (%)	9,6 \pm 0,3	10,0 \pm 0,2	NS
HOMA-IR	7,8 \pm 0,8	12,6 \pm 1,2	<0,002
HOMA-b-cell (%)	24,5 \pm 1,3	19,5 \pm 2,1	<0,04

BMI: Body mass index HbA1c: Glycated Hemoglobin NS: non-significative

Fasting and post-pandrial glucose behavior

Fasting glycemia: Significant differences were found ($p < 0,001$) between the non-insulin requiring group ($200 \pm 12,0$ mg/dl) and the insulin-requiring group ($291,5 \pm 17,6$ mg/dl). Figure 1, table 1.

Post-pandrial glycemia: When comparing the non-insulin requiring group ($266,05 \pm 17,67$ mg/dl) with the insulin requiring group ($361,6 \pm 26,1$ mg/dl), significant differences were observed ($p < 0,004$). Figure 1, table 1.

Fasting and post-pandrial insulin levels

No significant differences were found related to fasting insulin levels (non-insulin requiring group: $15,1 \pm 0,8$ μ U/ml Vs insulin requiring group $17,5 \pm 1,3$ μ U/ml), and neither were significant differences found when comparing post-pandrial insulin levels (non-insulin requiring group: $39,6 \pm 1,7$ μ U/m Vs insulin requiring group $40,2 \pm 3,8$ μ U/ml), $p = 0,1$. Figure 1, table 1.

Glycated hemoglobin levels (HbA1C)

No significant differences were seen when comparing HbA1c levels between the non-insulin requiring ($10,5 \pm 0,3\%$) Vs. the insulin requiring group ($12,6 \pm 1,2\%$), $p = 0,08$. Table 1.

HOMA_{IR} and HOMA _{β cell} Determination

HOMA-IR: Significant differences were observed ($p < 0,002$) between non-insulin requiring patients ($7,7 \pm 0,8$) vs. insulin requiring patients ($12,6 \pm 1,2$). Figure 1, table 1.

HOMA β -cell: Significant differences were found ($p < 0,04$) when comparing non-insulin requiring patients ($24,5 \pm 1,3$ %) vs. insulin requiring patients ($19,4$ % $\pm 2,4$). Figure 1, table 1.

DM is a serious and chronic metabolic disease with multiple complications and premature mortality, accounting for at least 10% of total health care expenditure in many countries^{3,35}. According to the 2004 data from the WHO, more than 150 million people around the world suffer from diabetes and projections estimate a further doubling in the first 25 years of the new millennium^{36,37}. However, the greatest increases in DM prevalence rates will be in developing nations such as Asia and Africa, where most of the diabetic patients will be diagnosed by 2025³⁷. The increase of diabetes mellitus incidence in developing countries follows the trend of urbanization and changes in lifestyle patterns and diet^{5,36}. Probably, the dramatic occurrence of DM will likely continue because of the growing prevalence of obesity^{5,38}.

Insulin resistance (IR), the leading abnormality in patients with DM-2 is characterized by the incapacity of insulin-sensitive tissues to respond to normal insulin circulating levels^{8,30}. Thus, in order to offset IR, pancreatic β -cells increase its insulin production and secretion. However, over time β -cell function deteriorates, less insulin is secreted, and hyperglycemia develops. In conclusion, DM-2 must be seen as a result of two main alterations: 1) peripheral IR which leads to both, hepatic fasting glucose over-production and post-pandrial muscle glucose uptake inhibition, and 2) secondary drop in insulin production via β -cell secretory dysfunction and apoptosis^{25,39,40}.

During DM-2 evolution, alterations in insulin secretory patterns (blunted first-phase insulin release) begin more than a decade before the disease is even diagnosed. Indeed, it is already present in normoglycemic first-degree relatives of DM-2 patients and people with impaired fasting glucose as a result of a complex interplay of genes and environment⁶. Hyperglycemia and free fatty acids behave as β -cell stressors acting via ceramide synthesis. This, in turn activates nitric oxide synthase expression, increasing nitric oxide concentrations and accelerating cellular apoptosis^{25,39,40,41}. In addition, free fatty acids may suppress the expression of genes responsible for stem cell formation in the pancreatic ducts. However, a recent study showed that apoptosis, rather than decreased β -cell formation, is the key event involved in the β -cell mass lost seen in DM-2^{25,40}. Therefore, the impact of pharmacological options on β -cells survival should be considered in order to improve the overall DM-2 control. In this sense, some studies conducted with tolbutamide and glyburide, have shown to activate apoptosis in β -cell lines and rodent islets, as well as in cultured human islets⁴²; by contrast, both nateglinide and repaglinide and thiazolidinediones (rosiglitazone or pioglitazone) have a markedly positive effect on β -cell survival⁴³. In addition, a recent study conducted by our group in type 2 diabetic individuals with a mean of 7 years of evolution since diagnosis and 50% β -cell reserve measured by HOMA _{β cell} showed a full recovery of pancreatic secretory capacity in the three intervention groups (diet alone, Metformin monotherapy and Glymepiride and Metfomin dual therapy)⁴⁴. Since metabolic disorders responsible for DM-2 coexist in the same individual, that is, muscle insulin resistance, hepatic insulin resistance and β -cell secretory dysfunction, we suggest that treatment should be reoriented to pharmacological management of those 3 conditions, altogether with a nutritional plan and physical activity that will promote weight loss in patients with overweight and obesity, diminishing free fatty acid offer to liver and muscle, avoiding insulin resistance in these tissues¹⁴.

It is interesting how this study design included patients with clinical insulinization criteria due to the

lack of response to oral therapy; however, it is even more impressive how these patients responded to double or triple-combination therapy with oral agents, that is, the addition of two sensitizers drugs such as Metformin¹⁰ (major effect on liver) and Rosiglitazone (major effect on muscle and adipose tissue)^{33,45}. The fact that 94% of all patients responded with normalized glycemic control parameters could be due to several elements. First of all, the responders group was in average younger and less insulin resistant than the non-responders group. Moreover, it is possible that the clinical criteria used till now lacks sensitivity and specificity enough to select accurately patients in which insulin therapy should be started immediately, and thus, many patients labeled as “insulin-requiring” are probably not^{28,29}. And second, monotherapy with oral agents, just as the UKPDS study points out, does not help accomplish euglycemic states for long periods of time, which is why a great deal of studies support moving on to combination therapy with oral agents in those individuals that do not respond to monotherapy¹⁶.

On the other hand, some authors propose early insulin administration as an alternative approach that may provide “ β -cell rest” and some degree of protection from apoptosis^{17,46}. Moreover, according to observational and interventional evidence, insulin therapy may preserve endothelial function and help to achieve a better glycemic control diminishing all retinopathy, progression of preexisting retinopathy, incidence of diabetic nephropathy and progression of diabetic neuropathy²⁴. Despite of this data, insulin treatment may have a dark face in DM-2 management. For instance, in the Veterans Affairs Cooperative Study in Type II Diabetes (VACS DM) 153 men with long-standing diabetes were randomly assigned to receive either standard insulin treatment (one morning injection daily) or intensive therapy combining dietary education and blood glucose self-monitoring⁴⁷. After 6 months, the mean HbA1c in the intensive therapy group was at or below 7.3% and remained 2% lower than the standard group for the duration of the trial, but there were 61 cardiovascular events in 40 patients and 10 deaths (6 due to cardiovascular causes) a higher number than expected for this group of patients.

In this framework, it is vital to clarify when a diabetic patient faces a non-return point in which β -cell function becomes irrecoverable or at least not sufficient enough to maintain a long lasting euglycemic state. All the above mentioned explains partially why insulin therapy initiation in DM-2 has stimulated scientific debate over the last five decades²⁹.

In our study, a statistical significant difference was found when comparing basal and post-pandrial glucose levels among non-insulin requiring type 2 diabetic patients and those that required initial in-

ulin therapy. Likewise, a significant difference was observed when comparing the degree of insulin resistance measured by HOMA_{IR} between non-insulin requiring type 2 diabetic patients and those that required initial insulin therapy in favor of the latter group. In this case, It is plausible that insulin resistance phenomena represents a heterogeneous entity affecting in a different degree the metabolic control in each patient, and in consequence, its role as pancreatic stressor may vary between each individual as its seen in both studied groups. Nevertheless, environmental and other genetic factors are not to be excluded as important inter-players in the final metabolic response characterized by hepatic glucose over production and altered glucose uptake by muscle following insulin receptor down-regulation and glucose transporters (GLUT-4) internalization¹¹⁻²¹.

Beta-cell vulnerability is strongly bounded to both genetic and environmental factors that could account for individual differences⁷, however, other factors such as free fatty acids and Resistin could also trigger transitory and permanent functional changes in β -cell secretory capacity^{10,48}. When comparing pancreatic β -cell function between the non-insulin requiring vs. insulin requiring patients, average HOMA _{β cell} was statistically superior for the non-insulin requiring group than the insulin requiring group. This finding suggest that those patients with HOMA _{β cell} values under 20% require immediate insulin therapy since normal laboratory parameters were not achieved using oral sensitizers, sulfonylurea, diet and exercise; whereas those with HOMA _{β cell} over 25% probably kept a functional pancreatic reserve capable of dealing with elevated glucose demands if combination therapy is started.

Patients that were incapable of responding to triple-combination therapy with oral agents have a different metabolic profile than those whom responded to treatment³⁴. This probably reflects an irreversible β -cell failure represented in their HOMA _{β cell} value (20%), showing that pancreatic β -cell is not able to normalize fasting nor post-pandrial plasmatic glucose levels but apparently is enough not to allow patients to fall into an extreme catabolic state (typical of a severe lack of insulin), which is commonly used as a clinical criteria to initiate insulin therapy, thus delaying the insulin therapy start²⁹. Taken together all the above mentioned and using them from a clinical perspective, patients that fulfill this pattern should initiate insulin therapy before evident fat and proteic weight loss occurs (Table 1). HOMA _{β cell} is able to distinguish β -cell functional capacity need to achieve glycemic control, at least during the follow up phase of this study. These patients are still being followed up in order to now if long term recovery of β -cell insulin secretory function can be achieved with triple combination therapy with oral agents with β -cell function of 25% or more.

HOMA _{β -cell} determination in the clinical practice is a useful tool to assess when insulin therapy should be started type 2 diabetic patients. Moreover, it minimizes insulin misuse in patients that could still benefit from combination therapy with oral agents^{13,26}.

Initiation of insulin therapy in type 2 diabetic patients must be sustained on clinical knowledge and the analysis of the precise metabolic situation of each individual. The latter one can be supported through the interpretation of all laboratory parameters currently available for these means; and in this sense the information provided by a simple easy to apply mathematical method, such as HOMA _{β -cell} is very valuable³¹. It provides information of pancreatic reserve and the possibility of a better outcome in type 2 diabetic patients under conventional therapies. Furthermore, the estimated pancreatic secretory capacity guarantees an effective reduction in the deleterious use of insulin therapy in patients who can positively respond to oral agents and assure instauration of insulin therapy in those with minimal pancreatic insulin reserve, which influences in the life quality of our patients.

This mathematical model also allows us to quantify insulin-resistance levels by estimating HOMA_{IR}, which is a key element in the follow up of the natural evolution of the disease and the evaluation of different treatment approaches.

We considerer convenient to quantify insulin levels as well as to estimate HOMA _{β -cell} and HOMA_{IR} in all type 2 diabetic patients not only in the means of diagnosis but also as a parameter to evaluate progression and therapeutic response in each patient. More studies that also support HOMA β -cell and HOMA-IR establishment as new criteria for initiating insulin therapy in type 2 diabetic patients are needed, so physicians can get more capable and comfortable with starting insulin programs.

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