Extreme subcutaneous insulin resistance: a misunderstood syndrome

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SUMMARY

Extreme subcutaneous insulin resistance (SIR) is a rare syndrome characterized by severe resistance to subcutaneous insulin with normal intravenous insulin sensitivity. Its pathophysiology is unknown, though an increased insulin degrading activity has been suggested. We report the case of a 35 year-old female patient with type I diabetes since the age of 3. Despite five shots of insulin/day, the patient progressively developed permanent ketosis related to severe acquired SIR with insulin doses as high as 500 U/day. Subcutaneous infusion of insulin and lispro insulin through an external pump did not improve resistance. HbA¹c levels remained between 14 and 18% (N < 6.5%). After numerous ketoacidotic episodes, continuous ambulatory intravenous insulin infusion was attempted through a central port due to a lack of peripheral venous access. HbAlc improved (8.5%) and daily insulin needs decreased to below 40U. However, the treatment had to be discontinued because of thrombosis and infection at different times. Intraperitoneal insulin infusion with an external pump was then proposed. HbAlc improved to 8% during 18 months but several episodes of catheter infection and encapsulation led to its removal. An intraperitoneal pump was surgically implanted, leading to the stabilization of HbA¹c to around 8%. An insulin degradation assay did not prove resistance. HbA¹c levels remained between 14 and 18% (N < 6.5%). After numerous ketoacidotic episodes, continuous ambulatory intravenous insulin infusion was attempted through a central port due to a lack of peripheral venous access. HbAlc improved (8.5%) and daily insulin needs decreased to below 40U. However, the treatment had to be discontinued because of thrombosis and infection at different times.

RÉSUMÉ

Insulino-résistance sous-cutanée extrême : un syndrome mal compris

L’insulino-résistance sous-cutanée extrême (SIR) est un syndrome rare caractérisé par une résistance sévère à l’insuline sous-cutanée alors que la sensibilité à l’insuline intraveineuse est normale. La physiopathologie en est inconnue bien qu’une dégradation accrue de l’insuline ait été suggérée. Nous rapportons le cas d’une jeune femme de 35 ans présentant un diabète de type 1 depuis l’âge de 3 ans. En dépit de 5 injections d’insuline par jour, la patiente développait progressivement une cétose permanente liée à un SIR extrême acquis avec des doses d’insuline aussi élevées que 500 unités par jour. L’infusion sous-cutanée d’insuline et de lispro à l’aide d’une pompe ambulatoire n’améliorait pas l’insulino-résistance. Les taux d’HbA¹c demeuraient entre 14 et 18% (N < 6.5%). Après de nombreux épisodes de cétoacidoses, l’injection intraveineuse continue ambulatoire d’insuline par l’intermédiaire d’un cathéter veineux central était tenté en raison de la perte de tout accès veineux périphérique. L’HbA₁c s’améliorait (8,5 %) et les besoins quotidiens en insuline descendaient à moins de 40U. Cependant, ce traitement devait être interrompu en raison d’épisodes répétés d’infection et de thrombose. Une infusion intrapéritonéale continue d’insuline était instaurée par l’intermédiaire d’une pompe externe. L’HbA₁c s’améliorait (8 %) pendant 18 mois mais plusieurs épisodes d’infection du cathéter et d’encapsulation conduisaient à son retrait. Une pompe intra-péritonéale était alors implantée chirurgicalement, conduisant à la stabilisation de l’HbA₁c, au voisinage de 8 %. Une mesure de la dégradation de l’insuline ne mettait pas en évidence d’accroissement de cette activité dans le tissu sous-cutané de la patiente par rapport aux témoins ; cependant des quantités excessives d’insuline étaient retrouvées dans le derme de cette patiente par rapport aux sujets contrôles. Ce cas clinique de SIR acquis soulève la question de son traitement et de ses mécanismes. Concernant le traitement, l’administration intra-péritonéale d’insuline semble la meilleure solution, mais les mécanismes demeurent mal élucidés.

Key-words: Subcutaneous insulin resistance - Insulin-degrading enzyme - Intraperitoneal pump.


Mots-clés : Résistance à l’insuline sous-cutanée · Enzyme de dégradation de l’insuline · Pompe intra-péritonéale.

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xtreme subcutaneous insulin resistance (SIR) is a rare syndrome characterized by severe resistance to subcutaneous insulin with normal intravenous insulin sensitivity. The first cases were reported in the seventies by Schneider [1] and Paulsen [2]. The pathophysiology of SIR is unknown. An increased insulin degrading activity has been reported in the subcutaneous adipose tissue fraction [2]. We report a diabetic patient having developed insensitivity to subcutaneous but not to intravenous insulin who was dramatically improved by intraperitoneal insulin. A study of subcutaneous adipose tissue insulin content was performed. The objective of this case report was to review the data found in literature and, following, to define the clinical context in which SIR is diagnosed, the specific investigations that should be performed, and the treatments available.

Case report

Case history

A 35-year-old female patient was referred for extreme insulin resistance when insulin was injected subcutaneously. Her family history included a mother with type 2 diabetes, while her personal history was marked by type 1 diabetes since the age of 3 with undetectable C peptide and HLA susceptibility DR1/DR4 to type 1 diabetes. No information about the balance of her diabetes during childhood was available. She had been referred to our department fifteen years ago because of poor glycemia control attributed to dietary indiscretions and inappropriate scheduling of insulin injections. Despite her compliance, imbalance progressively worsened with permanent life-threatening ketosis. It became obvious that ketosis could only be reduced via intravenous insulin therapy, since subcutaneous injections were totally ineffective. When the patient was referred to our department again, there was no sign of macroangiopathy but microangiopathy had appeared, characterized by laser-treated retinopathy, microalbuminuria and mild axonal neuropathy. Her body mass index was 32 kg/m² and waist/hip ratio < 0.85. Permanent ketosis was noted despite subcutaneous insulin doses as high as 500 U/day. The patient was hospitalized for months on account of numerous ketoacidotic episodes that occurred as soon as she was switched from intravenous insulin back to subcutaneous injections. Infections (urinary tract infection, sinusitis) were extremely frequent. Because of repeated antibiotic treatments and unbalanced diabetes, systemic candidosis developed. It was resistant to common antifungic drugs, and required intravenous antifungic treatment that induced transient nephrotoxicity.

Treatment

The follow-up of weight, glycated HbA1c and insulin delivery route is given in Figure 1. Briefly, subcutaneous injections of human insulin and lispro insulin analog were inefficient: HbA1c levels remained between 14 and 17.9% (N < 6.5%). Subcutaneous infusion of insulin through an external pump did not improve this resistance (HbA1c: 14.5%). After numerous ketoacidotic episodes and permanent ketosis, continuous ambulatory intravenous insulin infusion was attempted through an implanted venous access port due to a lack of peripheral venous access. HbA1c subsequently improved (8.5%) and daily insulin need decreased to below 40U. However, the treatment had to be discontinued because of thrombosis and infection at different times. Intrap-
eritoneal insulin infusion with an external pump (Diaport catheter) was then attempted. HbA1c decreased to 6.9% after a period of 18 months while weight dropped from 78 to 65 kg. At this time, the loss of this first catheter, followed by several episodes of infection and encapsulation of the second and third catheters led to their removal. While the patient was waiting for an implanted pump, another attempt of central venous port was made but soon failed. Finally, a pump delivering intraperitoneal insulin (MIP, 2001) was implanted, which led to stable levels of HbA1c around 8-8.5% during 12 months. Insulin needs averaged 30 to 40 U/day.

Causes of insulin resistance

This patient had none of the known causes of insulin resistance, whether physiological or pathological. She had no hormonal dysregulation, no increase in the circulating antibodies to insulin or to insulin receptors. Her sensitivity to intravenous insulin was not in favor of a genetic cause. She had neither lipo-dystrophy, atrophy nor dyslipidemia. Plasma levels of adipokines such as PAI-1 (0 UI/ml-N < 16) and interleukine 6 (12.3pg/ml-N < 20) were normal, as was the urinary THE/THF ratio reflecting 11-betahydroxysteroid dehydrogenase activity. Increased plasma leptin levels (33 ng/ml-N; 7.4 ± 3.7) related to her mild obesity were noted. No evidence of surreptitious administration of insulin could be found. An insulin challenge testing comparing insulinemia after 0.1 or 0.5 units of insulin/kg of body weight, injected either subcutaneously or intravenously, was performed with difficulties in reason of very poor peripheral veins. The results (Fig 2) showed 1) a significant decrease of glycolysis only when insulin was injected intravenously by comparison with subcutaneous injections whatever the dose; 2) higher insulinemia levels with insulin injected intravenously by comparison with subcutaneous injections whatever the dose; 2) higher insulinemia levels with intravenous than with subcutaneous route. Therefore we suspected severe subcutaneous insulin resistance related to a possible excess of insulinase and undertook a study of subcutaneous tissues.

Study of subcutaneous tissue

Methods

Specimens

The subcutaneous injections of insulin were withheld for more than 3 weeks before sampling. Having obtained the informed consent of the patient, subcutaneous biopsy specimens were taken from the periumbilical region when the pump was implanted, rinsed briefly in cold isotonic sodium chloride, immediately chilled to 4 °C and frozen within one hour at – 20 °C. Control subcutaneous biopsy specimens were also obtained in two non diabetic, non obese women who had undergone other surgical procedures.

Preparation of tissue extracts

Measurement of insulin proteolytic activity and insulin content was performed in tissue extracts (adipose tissue and derm). The homogenization of samples was adapted from Poulsen et al. [2] and Tetaert et al. [3]. Thawed samples were homogenized in a 200 mM sucrose -250 mM NaCl solution (1ml per gram of tissue) at 4°C using a Potter-Elvehjem teflon-glass homogenizer and centrifuged at 3300 g for 15 minutes at 4 °C. The sucrose solutions were collected. Moreover, the fat layer (for the adipose tissue homogenates) and the particulate pellet (for the derm homogenates) were resuspended in 1 ml of the sucrose-NaCl solution + 0.1% Triton X-100/gram and incubated at room temperature on a rotating mixer for one hour before centrifugation at 3300 g for 15 minutes at 4 °C. The Triton was used at 0.1% in order to lyse the intact cellular structures since this concentration did not inhibit the insulinase activity from haemolysed sera (data not shown). The sucrose solutions were collected again. The protein content of each of these soluble extracts was determined by the method of Bradford [4] using the Bio-Rad Protein assay kit (Biorad, Ivry s/Seine, France) with bovine serum albumin as reference standard. Before measuring the insulin degrading activity, the fractions were diluted in the sucrose-NaCl solution in order to get a protein concentration of 2 g/l.

Insulin degradation assay

Incubation conditions were adapted from Shearet et al. [5]. Briefly, for each of the tissue extracts, we incubated at 37 °C for 60 minutes: (I) 100 µl of a 500 mU/l insulin standard solution with (II) 40 µl of 20 mM 2-(N-Morpholino)ethanesulfonic acid (pH 7.5) (Sigma, St. Louis, MO, USA) containing 1.5 mM MgCl2, 5 mM KCl and 0.5% bovine serum albumin, (III) 50 µl of the sucrose-NaCl solution, and (III) 10 µl of the diluted soluble extracts. The reaction was stopped by the addition of 10 µl of a 50 mM p-hydroxymercuribenzoic acid (Sigma, St. Louis, MO, USA) in 0.02 N NaOH/water solution and the incubation media were immediately frozen at – 80 °C. The insulin concentration of each preparation was measured before and after the incubation using a radioimmunometric sandwich assay (Bi-Insulin IRMA, Cis-Bio International, Gif sur Yvette, France). In these incubation conditions we were able to evidence a 16.4% degradation of the added insulin in 60 minutes at 37 °C using a haemolysed serum (hemoglobin: 2.7g/l) instead of soluble extracts. Moreover, the insulin concentration of the soluble extracts was assayed using the same kit.

Results

Insulin degradation assay

The recovery of insulin was about 100% whatever the extract we tested. Consequently, these results did not evidence any insulin degrading activity in the tissues of the patient (Tab I).
Insulin concentration in the tissues

The insulin levels yielded by the IRMA kit were higher in the soluble extracts of the patient than in the control ones. Moreover, we observed in the patient that the insulin concentrations are higher in the derm extracts than in the adipose tissue extracts (Tab II). These results are in favor of an insulin sequestration in the derm.

Discussion

The case we present had type 1 diabetes documented by young age of occurrence, undetectable C peptide and genetic susceptibility. The patient progressively developed extreme insulin resistance as demonstrated by repeated infections and numerous ketoacidotic episodes when insulin was given subcutaneously, but she remained sensitive to intravenous insulin.

About 20 to 25 cases of diabetic patients with insensitivity to subcutaneous but not intravenous insulin have been reported in literature [1, 2, 7-19] (Tab III). As in our case, most of the reported patients were young women with insulin-dependent diabetes. Their subcutaneous insulin resistance was revealed by numerous DKA or permanent ketonuria and recurrent infections. It sometimes was simply transient, and sometimes transient and recurrent. In 1979, Paulsen [2] rigorously defined this syndrome according to three criteria: 1) resistance to the hypoglycemic action of subcutaneous insulin, but not to intravenous insulin, associated with 2) lack...
of increase in the plasma of free-insulin levels after subcutaneous insulin and 3) increased insulin-degrading activity in the subcutaneous tissue. While the first criteria is present in all published observations, less than half of the previously reported patients fit the second criteria. Moreover, in literature, a search for insulin degrading activity in subcutaneous tissue was performed in less than one out of five patients.

Therefore, because of frequent incomplete diagnosis criteria, differential diagnosis with brittle diabetes, sometimes factitious, is very difficult [20, 21]. Moreover, it is known that physiological degradation of insulin in subcutaneous tissue may greatly vary from one patient to another and from day to day, especially according to the site and depth of injections and skin temperature. These hypotheses cannot be eliminated in our case. In this case, the weight gain observed before pump implantation is surprising. It could be explained by lack of exercise due to long-lasting hospitalizations and/or massive and repeated doses of insulin that were given intravenously during ketoacidotic episodes. Nevertheless the possibility of associated eating disorders and/or factitious brittle diabetes can not be discarded.

The existence of a SIR syndrome implies that the absorption of insulin injected into subcutaneous tissue is inhibited to a greater extent than could be accounted for by normal variations in insulin absorption. The mechanisms are not clear but excessive degradation or sequestration of insulin at the site of injection could be involved [22]. The presence of a heat-labile insulin-degrading activity has been demonstrated in subcutaneous adipose tissue, muscle or sera of some patients during a period of subcutaneous insulin resistance [2, 12, 13]. The disappearance of this insulin-degrading activity during the periods of insulin sensitivity was checked in at least one case [13]. A tritiated-insulin absorption test has also shown abnormalities in insulin degradation products [10]. Contrasting with these data some authors have found large amounts of insulin in subcutaneous tissue, associated with very severe hypoglycemias that rather suggest that insulin accumulated [11]. Nevertheless, in 1986, Schade [20] studied a series of 16 patients with apparent SIR syndrome according to a strictly controlled protocol following Paulsen’s criteria and completed the study with a tritiated-insulin absorption study (Tab IV). He was unable to demonstrate any defect of insulin absorption or the presence of insulin degrading enzyme in any patients. Two of the patients in his series had been previously reported by Freidenberg [11] and successfully treated with aprotinin and then infraarterioenal insulin. In several reports, the effectiveness of aprotinin, a protease inhibitor, has been considered as arguing for the hypothesis of excessive degradation by subcutaneous proteases. In our case, we found very high levels of insulin in the subcutaneous tissue of the patient as in Freidenberg’s case report [11]. However our patient never experimented hypoglycemia and we were unable to demonstrate any increase of insulin-degrading activity.

Insulin degradation is a regulated process that includes the uptake, processing and degradation of the hormone [23, 24]. It is mediated through a multifonctional insulin degrading enzyme (IDE) which is an intracellular binding, regulatory and degradative protein controlling insulin action in association with other systems such as lysosomes and other enzymes. IDE is a sulphydryl-dependant metalloproteinase with a zinc-binding site. This component of a cytosolic proteolytic complex is relatively specific for a number of growth factors and hormones, such as insulin, ANP, IgF1, amylin, and proinsulin. It increases proteasome and steroid hormone receptor activity, a procedure that is reversed by insulin. Proteasome, a multicatalytic proteinase (MCP) is believed to be important in non-ubiquitin pathways of cellular protein degradation.

Table I
Insulin concentrations in incubation media after 60 minutes at 37°C. The results are expressed as percentages of initial insulin concentrations in the media before the incubation.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Control patient</th>
<th>Control patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual insulin in whole adipose tissue soluble extract (%)</td>
<td>108</td>
<td>101</td>
<td>96</td>
</tr>
<tr>
<td>Residual insulin in fat layer soluble extract (%)</td>
<td>103</td>
<td>101</td>
<td>ND</td>
</tr>
<tr>
<td>Residual insulin in whole derm soluble extract (%)</td>
<td>104</td>
<td>106</td>
<td>ND</td>
</tr>
<tr>
<td>Residual insulin in derm particulate pellet soluble extract (%)</td>
<td>100</td>
<td>102</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not determined.

Table II
Insulin concentration (mUI/g protein) in the tissue soluble extracts of the diabetic patient and the non diabetic control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Control patient 1</th>
<th>Control patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin concentration in whole adipose tissue soluble extract (mUI/g)</td>
<td>846</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Insulin concentration in fat layer soluble extract (mUI/g)</td>
<td>477</td>
<td>1.5</td>
<td>ND</td>
</tr>
<tr>
<td>Insulin concentration in whole derm soluble extract (mUI/g)</td>
<td>1098</td>
<td>1.5</td>
<td>ND</td>
</tr>
<tr>
<td>Insulin concentration in derm particulate pellet soluble extract (mUI/g)</td>
<td>1406</td>
<td>6</td>
<td>ND</td>
</tr>
</tbody>
</table>

ND: not determined.
degradation [25]. There is a direct insulin/IDE interaction that may modulate fat and protein turnover by inhibiting protein degradation [26]. Last, the IDE/MCP complex can be purified by affinity, conventional or ion exchange chromatography [27]. As of today, it is not well known whether IDE and insulin-degrading activity are the same enzymes, even though it has been suggested previously [28].

Suggested treatments of SIR are based on either additives to prevent enzymatic degradation or alternative routes of insulin delivery. Among additives, protease inhibitors [9, 10, 

Table III
Cases of subcutaneous insulin resistance reported in literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Patients/age (years)/gender</th>
<th>SC resistance IV sensitivity</th>
<th>Levels of free insulin tested</th>
<th>Insulin degrading activity</th>
<th>Tritiated-insulin study</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneider [1]</td>
<td>1/16/F ketosis transient</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>IV injections/infusion (+)</td>
</tr>
<tr>
<td>Paulsen [2]</td>
<td>1/17/F DKA/infections transient</td>
<td>yes</td>
<td>yes</td>
<td>present in sera/SC tissue</td>
<td>ND</td>
<td>IV infusion (+)</td>
</tr>
<tr>
<td>Dandona [7]</td>
<td>1/14/F</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Aprotinine/SC injection (+)</td>
</tr>
<tr>
<td>Henry [8]</td>
<td>1/18/F</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Aprotinine (+)</td>
</tr>
<tr>
<td>Müller [9]</td>
<td>1/52/F DKA/infections transient</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>IV infusion (±)</td>
</tr>
<tr>
<td>Mc Elduff [10]</td>
<td>1/16/F transient</td>
<td>yes</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>IV infusion (±)</td>
</tr>
<tr>
<td>Misbin [12]</td>
<td>1/24/M</td>
<td>yes</td>
<td>Present in sera</td>
<td>ND</td>
<td>ND</td>
<td>IM injections (+)</td>
</tr>
<tr>
<td>Maberly [13]</td>
<td>1/20/F DKA/infections transient</td>
<td>yes</td>
<td>yes</td>
<td>Increased in adipose tissue and muscle</td>
<td>ND</td>
<td>SC infusion (−) IM injections (−) Aprotinine/SC (−) or IV insulin (+)</td>
</tr>
<tr>
<td>Shade [14]</td>
<td>3/15 to 27/2F-1M</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>IP infusion (+)</td>
</tr>
<tr>
<td>Campbell [15]</td>
<td>1/22/F DKA/infections</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>IP/IP (+)</td>
</tr>
<tr>
<td>Blazar [16]</td>
<td>1</td>
<td></td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Chloroquine</td>
</tr>
<tr>
<td>Dandonna [17]</td>
<td>2</td>
<td>yes</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>IP infusion (+)</td>
</tr>
<tr>
<td>Brossard [18]</td>
<td>1/26DKA</td>
<td>yes</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td>IV infusion (±) IP infusion (±) IM injections (±) SC infusion (−) with regular, freeze-dried and lispro insulin IV infusion (±) Aprotinine/SC insulin infusion (−) IP/IP (+)</td>
</tr>
<tr>
<td>Riveline [19]</td>
<td>1/36/M AP/hyperosmolar</td>
<td>yes</td>
<td>yes</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SC: subcutaneous; IV: intravenous; IP: intraperitoneal; IPIP: intraperitoneal implanted pump; (+): effective; (−): ineffective; (±): effective but complications; DKA: diabetic ketoacidosis; AP: acute pancreatitis.
Aprotinine is a protease inhibitor that has been used in the treatment of acute pancreatitis, chronic urticaria, acne and fibrinolysis. It is a polypeptide of 58 amino acids initially obtained from bovine lung and parotid gland. Aprotinine enhances absorption by inhibiting insulinase and increasing vasodilation. The side effects most frequently reported are nausea, vomiting, diarrhea and myalgia but also hypoglycemia and anaphylaxis. The main commercially available products are Trasylol® (Bayer Laboratory) or Iniprol® (Choay, Gentilly, France) used at a final dilution of 4 to 160 kallikrein-inactivity units (KIU)/Unit of insulin [11], mixed with insulin, either subcutaneously or intravenously over a period of 30 minutes every 8 hours. It forms a cloudy suspension when it is mixed with insulin. Otherwise, chloroquine [16] used as an enzyme inhibitor and plasmapheresis [30] have been used only once each, which is why their effectiveness is difficult to assess. Among other routes of insulin delivery, intramuscular insulin therapy [12, 13, 18, 31] has been used during periods of at least one year, but with a risk of fibrosis. Intravenous insulin therapy [2, 7, 11, 18, 19], either by continuous infusion from an external pump or by intravenous bolus injections every two hours through an indwelling venous access needle is a temporary yet reasonable solution. Nevertheless, the risk of thrombosis, sepsis and catheter breakage is major. Last, peritoneal devices [14, 15, 17, 19] have been found to be effective in 7 of the 8 previously published cases. Two of them were treated with an implantable pump [15, 19].

**Conclusion**

This case report of acquired SIR raises the question of accurate diagnosis according to Paulsen’s and Schade’s criteria. These criteria have rarely been respected in literature because of the scarcity of cases. The treatment of SIR remains difficult even if intraperitoneal delivery of insulin today appears to be the safest solution. And last, mechanisms of SIR still remain unclear even if excessive degradation or sequestration of insulin is probably involved.

**References**