SCIENTIFIC OBSERVATIONS
Correlation between CCL20 and serum glucose in postoperative coronary bypass patient: A call for further investigation

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ABSTRACT
Insulin administration during cardiopulmonary bypass grafting (CABG) and in the perioperative period has been shown to lower TNF-α, IL-6, and IL-8 levels, which are considered to be mediators of immunity and inflammation. It is not known whether perioperative hyperglycemia attenuates the action of lymphocyte attracting chemokines such as CCL20 ([CC-motif] ligand 20), also known as macrophage inflammatory protein 3, MIP-3α; or liver activation regulated chemokine, LARC. CCL20 is a selective chemoattractant for immature dendritic cells, effector/memory T lymphocytes and naïve B cells, and is recognized as a critical regulator of both innate and acquired immunity. In this report, we describe our preliminary findings related to the interaction between serum blood glucose and CCL20. Specifically, we report an increase in CCL20 temporally associated with improving glycemic control in a diabetic patient undergoing intensive insulin therapy after open heart surgery.

INTRODUCTION
In postoperative cardiac surgery patients, hyperglycemia has been associated with increased levels of TNFα in peripheral blood. 1-4 Insulin administration during cardiopulmonary bypass grafting (CABG) and the perioperative period has been shown to lower TNF-α, IL-6, and IL-8 levels, which are considered to be mediators of immunity and inflammation. 5 It is not known whether perioperative hyperglycemia attenuates the action of lymphocyte attracting chemokines such as CCL20 ([CC-motif] ligand 20), also known as macrophage inflammatory protein 3, MIP-3α; or liver activation regulated chemokine, LARC. CCL20 is a selective chemoattractant for immature dendritic cells, effector/memory T lymphocytes and naïve B cells, and is recognized as a critical regulator of both innate and acquired immunity. 6 CCL20 is involved in the formation and function of mucosal lymphoid tissues via chemotraction of lymphocytes and dendritic cells to epithelial cells surrounding these tissues. It binds and activates chemokine receptor CCR6. CCL20 is upregulated in the wound healing of mouse gingiva and in postoperative total hip arthroplasties. 7,8 It is also induced in human keratinocytes by electric fields of 100-300 mV/mm and is upregulated by human gingival fibroblasts upon stimulation with cytokines and bacterial endotoxin. CCL20 is thought to recruit immature dendritic cells to skin wound sites. 9,10 In this report, we describe our preliminary findings related to the interaction between serum blood glucose and CCL20. Specifically, we report increasing levels of CCL20 that temporally correlated with improving glycemic control in a diabetic patient undergoing intensive insulin therapy for hyperglycemia after open heart surgery.

CASE REPORT
An 82-year-old hypertensive, diabetic, female had undergone three-vessel coronary artery bypass grafting. She was a participant in an Institutional Review Board-approved protocol in which, in addition to glucose point-of-care testing (nurses performing finger sticks), her interstitial tissue was sampled by a continuous glucose monitoring system (Medtronic Diabetes CGMS Ipro®, Northridge, CA). The patient was initially placed on an insulin sliding scale regimen with subcutaneous injections, with early therapeutic failure (i.e., glucose level 244 mg/dl shortly after initiation of therapy). The decision was made to begin insulin infusion with additional glucose level sampling via point-of-care testing.

After patient consent for additional sampling was granted, five 3-milliliter blood samples were collected at 120-150 minute intervals (over 525 minutes) with measurements of CCL20 and TNF-α by ELISA (enzyme linked immunosorbent assay), and NF-κB by western blot. The results are listed in Table 1. The initial sample was drawn before the insulin infusion was started. As can be seen, serum levels of CCL20 demonstrated an inverse relationship to both serum glucose and to TNFα levels.

<table>
<thead>
<tr>
<th>Blood Sample</th>
<th>Time (hour)</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (units/hr)</th>
<th>CCL20 (pg/ml)</th>
<th>TNF-α (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8:40</td>
<td>244</td>
<td>0.6</td>
<td>19.2</td>
<td>6.6</td>
</tr>
<tr>
<td>2</td>
<td>10:40</td>
<td>210</td>
<td>3.5</td>
<td>24.1</td>
<td>2.3</td>
</tr>
<tr>
<td>3</td>
<td>12:47</td>
<td>126</td>
<td>6.5</td>
<td>42.4</td>
<td>1.1</td>
</tr>
<tr>
<td>4</td>
<td>15:15</td>
<td>90</td>
<td>0.0</td>
<td>50.1</td>
<td>1.1</td>
</tr>
<tr>
<td>5</td>
<td>15:25</td>
<td>123</td>
<td>43.8</td>
<td>43.8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

mg = milligrams; d = decliners; pg = picograms; hr = hour

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DISCUSSION
These results bring forth interesting questions regarding the relationship of insulin and/or glycemic control and the behavior of serum CCL20 levels. Our finding may be of importance in the areas immunomodulation and wound healing. Furnary et al established that continuous insulin infusions decreased deep sternal wound infection rates in diabetic CABG patients despite the fact that the interventional group had more morbid obesity and increased rates of intrathoracic conduit placement. Estrada et al showed that hyperglycemia in any CABG patient could result in longer hospitalization and increased costs. This work was followed by findings that high-dose insulin therapy attenuates inflammation in the early postoperative period as demonstrated by decreased levels of IL6, IL8, and TNFα, and that TNFα increases cell apoptosis, and impairs wound healing in diabetic patients. Hosokawa et al found that in periodontal tissue IL8, TNFα, and E. coli lipopolysaccharide induce CCL20. These cytokines may universally induce CCL20 in humans. It is important to note that same investigators also demonstrated that vascular endothelial growth factor (VEGF) levels were higher in cultures treated with CCL20. VEGF serves as a cellular signal that stimulates new blood vessel growth and enhances oxygen supply to tissues when there is inadequate circulation. Additionally, Buvanendran et al have recently demonstrated that CCL20 gene expression, from wound samples collected 24 hours postoperatively, is upregulated after total hip arthroplasty, although its role (other than being a strong lymphocyte chemoattractant and weak recruiter of neutrophils) could not be elucidated in that study.

CONCLUSIONS
The above case report suggests that insulin therapy and improved glycemic control may be associated with decreased serum TNFα levels and increased CCL20 levels. In postoperative cardiac surgery patients, this may be of importance because of the known relationship between hyperglycemia and impaired wound healing, among other factors. Specific areas for additional research include the potential role of CCL20 in postoperative wound healing and immunity (especially in diabetic patients), as well as clarification of the signaling pathways that result in the upregulation of CCL20 (specifically through the activation of Toll-like receptor 2 (TLR2) and TRAF6, MyD88, and NF-κB).

REFERENCES

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